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The 4th day of September 2007

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The subject of the present invention is novel 1,2,3-substituted indolizine derivatives, which are selective inhibitors of b-FGF (basic fibroblast growth factors), the method for preparing them and the pharmaceutical compositions containing them.

FGFs are a family of polypeptides which are synthesized by a large number of cells during embryonic development and by cells of adult tissues under various pathological conditions.

Some derivative of naphthyridinediamines and corresponding ureas are known which are selective inhibitors of FGF-1 (Batley B. et al., *Life Sciences*, (1998), Vol. 62 No. 2, pp. 143-150; Thompson A. et al., *J. Med. Chem.*, (2000), Vol. 43, pp. 4200-4211).

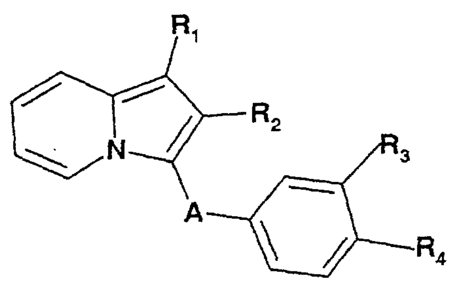
Some indolizine derivatives are described in Patent Applications and Patents US 4 378 362, FR 2 341 578, GB 2 064 536, EP 0 097 636, EP 302 792, EP 0 382 628, and EP 0 235 111. These compounds are useful in the treatment of angina pectoris and arrhythmia. Calcium translocation inhibiting properties are described for some of these compounds.

Patent Application EP 0 022 762 also describes some indolizine derivatives which possess a xanthine oxidase and adenosine deaminase inhibiting activity and a uricosuric activity. These compounds may be used in the treatment of physiological disorders

which occur following an excess of uric acid, disruptions of the immune system and as parasitic agents.

It has now been found that some compounds, derived from indolizine, are potent antagonists of the binding of b-FGF to its receptors.

Accordingly, the subject of the present invention is novel indolizine derivatives of formula I,



(I)

in which

- **R_1** represents a hydroxyl radical, a linear or branched alkoxy radical of 1 to 5 carbon atoms, a carboxyl radical, an alkoxycarbonyl radical of 2 to 6 carbon atoms or a radical of formula:
  - $-NR_5R_6$
  - $-NH-SO_2-Alk$
  - -NH-CO-Ph
  - -NH-CO-Alk
  - $-NH-CO_2-Alk$
  - $-O-(CH_2)_n-cAlk$

- -O-Alk-$COOR_7$
- -O-Alk-O-R_8
- -O-Alk-OH
- -O-Alk-C(NH_2):NOH
- -O-Alk-NR_5R_6
- -O-Alk-CN
- -O-$(CH_2)_n$-Ph
- -O-Alk-CO-NR_5R_6
- -CO-NH-$(CH_2)_m$-$COOR_7$
- -CO-NH-Alk
- -CO-NH-Ph

in which

- Alk represents an alkyl radical or a linear or branched alkylene radical of 1 to 5 carbon atoms,
- cAlk represents a cycloalkyl radical of 3 to 6 carbon atoms,
- n represents an integer from 0 to 5,
- m represents an integer from 1 to 5,
- R_5 and R_6, which are identical or different, each represent a hydrogen atom, a linear or branched alkyl radical of 1 to 5 carbon atoms or a benzyl radical,
- R_7 represents a hydrogen atom or an alkyl radical of 1 to 5 carbon atoms,

- R_8 represents an alkyl radical of 1 to 5 carbon atoms or a radical -CO-Alk,
- Ph represents a phenyl radical which is optionally substituted with one or more halogen atoms, with one or more alkoxy radicals of 1 to 5 carbon atoms, with one or more carboxyl radicals or with one or more alkoxycarbonyl radicals of 2 to 6 carbon atoms,

- **R_2** represents an alkyl radical of 1 to 5 carbon atoms, a cycloalkyl radical of 3 to 6 carbon atoms or a phenyl radical which is optionally substituted with one or more halogen atoms, with one or more alkoxy radicals of 1 to 5 carbon atoms, with one or more carboxyl radicals or with one or more alkoxycarbonyl radicals of 2 to 6 carbon atoms,
- **A** represents a radical -CO-, -SO- or $-SO_2-$,
- **R_3** and **R_4**, which are identical or different, each represent a hydrogen atom, an alkoxy radical of 1 to 5 carbon atoms, an amino radical, a carboxyl radical, an alkoxycarbonyl radical of 2 to 6 carbon atoms, a hydroxyl radical, a nitro radical, a hydroxyamino radical, a radical of formula
  - $-Alk-COOR_7$
  - $-NR_5R_6$
  - $-NH-Alk-COOR_7$

- -NH-COO-Alk
- $-N(R_{11})-SO_2-Alk-NR_9R_{10}$
- $-N(R_{11})-SO_2-Alk$
- $-N(R_{11})-Alk-NR_5R_6$
- $-N(R_{11})-CO-Alk-NR_9R_{10}$
- $-N(R_{11})-CO-Alk$
- $-N(R_{11})-CO-CF_3$
- -NH-Alk-HetN
- $-O-Alk-NR_9R_{10}$
- $-O-Alk-CO-NR_5R_6$
- -O-Alk-HetN

in which n, m, Alk, R_5, R_6 and R_7 have the meaning given above for R_1, and

- R_9 and R_{10}, which are identical or different, each represent a hydrogen atom or an alkyl radical of 1 to 5 carbon atoms,
- R_{11} represents a hydrogen atom or a radical $-Alk-COOR_{12}$ where R_{12} represents a hydrogen atom, an alkyl radical of 1 to 5 carbon atoms or a benzyl radical,
- HetN represents a 5- or 6-membered heterocycle containing at least one nitrogen atom and optionally another heteroatom chosen from nitrogen and oxygen,

or R_3 and R_4 form together a 5- to 6-membered unsaturated heterocycle, provided, however, that

when R_3 represents an alkoxy radical and R_4 represents a radical -O-Alk-NR_9R_{10} or a hydroxyl radical, R_1 does not represent an alkoxy radical, optionally in the form of one of their pharmaceutically acceptable salts.

A compound of formula I is preferred in which

- **R_1** represents a hydroxyl radical, a linear or branched alkoxy radical of 1 to 5 carbon atoms, a carboxyl radical, an alkoxycarbonyl radical of 2 to 6 carbon atoms or a radical of formula:
  - -NR_5R_6
  - -NH-SO_2-Alk
  - -NH-CO-Ph
  - -NH-CO-Alk
  - -NH-CO_2-Alk
  - -O-$(CH_2)_n$-cAlk
  - -O-Alk-$COOR_7$
  - -O-Alk-O-R_8
  - -O-Alk-OH
  - -O-Alk-NR_5R_6
  - -O-Alk-CN
  - -O-$(CH_2)_n$-Ph
  - -O-Alk-CO-NR_5R_6
  - -CO-NH-$(CH_2)_m$-$COOR_7$
  - -CO-NH-Alk
  - -CO-NH-Ph

in which

- Alk represents an alkyl radical or a linear or branched alkylene radical of 1 to 5 carbon atoms,
- cAlk represents a cycloalkyl radical of 3 to 6 carbon atoms,
- n represents an integer from 0 to 5,
- m represents an integer from 1 to 5,
- R_5 and R_6, which are identical or different, each represent a hydrogen atom, a linear or branched alkyl radical of 1 to 5 carbon atoms or a benzyl radical,
- R_7 represents a hydrogen atom or an alkyl radical of 1 to 5 carbon atoms,
- R_8 represents an alkyl radical of 1 to 5 carbon atoms or a radical -CO-Alk,
- Ph represents a phenyl radical which is optionally substituted with one or more halogen atoms, with one or more alkoxy radicals of 1 to 5 carbon atoms, with one or more carboxyl radicals or with one or more alkoxycarbonyl radicals of 2 to 6 carbon atoms,

- **R_2** represents an alkyl radical of 1 to 5 carbon atoms, a cycloalkyl radical of 3 to 6 carbon atoms or a phenyl radical which is optionally substituted with one or more halogen atoms, with

one or more alkoxy radicals of 1 to 5 carbon atoms, with one or more carboxyl radicals or with one or more alkoxycarbonyl radicals of 2 to 6 carbon atoms,

- **A** represents a radical -CO- or $-SO_2-$,
- $\mathbf{R_3}$ and $\mathbf{R_4}$, which are identical or different each represent a hydrogen atom, an alkoxy radical of 1 to 5 carbon atoms, an amino radical, a carboxyl radical, an alkoxycarbonyl radical of 2 to 6 carbon atoms, a nitro radical, a hydroxyamino radical, a radical of formula
  - $-Alk-COOR_7$
  - $-NR_5R_6$
  - $-NH-Alk-COOR_7$
  - -NH-COO-Alk
  - $-N(R_{11})-SO_2-Alk-NR_9R_{10}$
  - $-N(R_{11})-SO_2-Alk$
  - $-N(R_{11})-Alk-NR_5R_6$
  - $-N(R_{11}-CO-Alk-NR_9R_{10}$
  - $-N(R_{11})-CO-Alk$
  - -NH-Alk-HetN

  in which n, m, Alk, R_5, R_6 and R_7 have the meaning given above for R_1, and
  - R_9 and R_{10}, which are identical or different, each represent a hydrogen atom or an alkyl radical of 1 to 5 carbon atoms,

- R_{11} represents a hydrogen atom or a radical -Alk-$COOR_{12}$ where R_{12} represents a hydrogen atom, an alkyl radical of 1 to 5 carbon atoms or a benzyl radical,
- HetN represents a 5- or 6-membered heterocycle containing at least one nitrogen atom and optionally another heteroatom chosen from nitrogen and oxygen,

optionally in the form of one of their pharmaceutically acceptable salts.

A compound of formula I is particularly preferred in which

- **R_1** represents an alkoxy radical of 1 to 5 carbon atoms, a carboxyl radical, a radical -O-Alk-COOH in which Alk represents a linear or branched alkylene radical of 1 to 5 carbon atoms, a radical of formula -O-Alk-Ph in which Alk represents an alkylene radical of 1 to 5 carbon atoms and Ph represents a phenyl radical which is optionally substituted with one or more halogen atoms or with one or more alkoxy radicals of 1 to 5 carbon atoms or with one or more carboxyl radicals, a radical of formula -NH-CO-Ph or a radical of formula -CO-NH-Ph,

- **R_2** represents an alkyl radical of 1 to 5 carbon atoms,

- **A** represents a radical -CO-,
- **R_3** and **R_4**, which are different, each represent a hydrogen atom, an alkoxy radical of 1 to 5 carbon atoms, an amino radical, a carboxyl radical or an alkoxycarbonyl radical of 2 to 6 carbon atoms,

optionally in the form of one of its pharmaceutically acceptable salts.

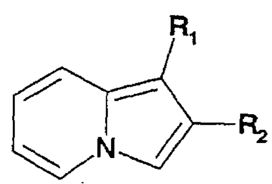
Among the compounds of the invention, the compounds which are particularly preferred are the following:

- (4-amino-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone
- 3-(4-amino-3-methoxybenzoyl)-2-methylindolizin-1-yl carboxylic acid
- 2-{[3-(4-amino-3-methoxybenzoyl)-2-methylindolizin-1-yl]oxy}acetic acid
- (4-amino-3-methoxyphenyl){1-[(4-chlorobenzyl)-oxy]-2-methylindolizin-3-yl}methanone
- (4-amino-3-methoxyphenyl){1-[(3-methoxybenzyl)oxy]-2-methylindolizin-3-yl}methanone
- 4-({[3-(4-amino-3-methoxybenzoyl)-2-methylindolizin-1-yl]oxy}methyl)benzoic acid
- 3-(4-carboxybenzoyl)-2-methylindolizin-1-yl carboxylic acid

- methyl 3-[(1-methoxy-2-methylindolizin-3-ylcarbonyl]benzoate
- 4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]benzoic acid

optionally in the form of one of its pharmaceutically acceptable salts.

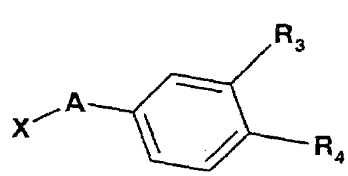
The present invention also relates to a method for preparing the compounds of formula I, characterized in that an indolizine derivative of formula II,



(II)

in which R_1 and R_2 have the meaning given for formula I,

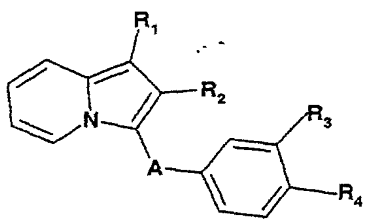
is condensed with a derivative of formula III,



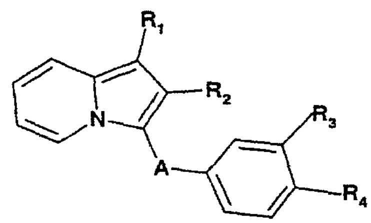
(III)

in which R_3 or R_4, which are identical or different, each represent a hydrogen atom, a nitro radical or an

alkoxycarbonyl radical of 2 to 6 carbon atoms, in order to obtain the compounds of formula Ia or Id,



(Ia)

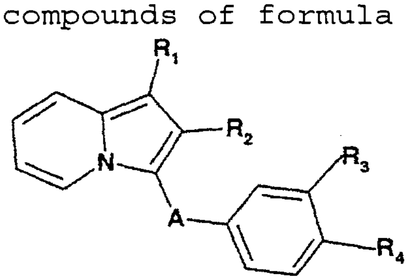


(Id)

R_3 and/or R_4 = $-NO_2$ **R_3 and/or R_4 = $-CO_2$Alkyl**

and then,

a) in that the compounds of formula Ia are subjected to a reduction in order to obtain the compounds of formula Ib,



(Ib)

R_3 and/or R_4 = $-NH_2$

in which R_3 and/or R_4 represent an amino radical, which compounds of formula Ib then

- are subjected to the action of an alkyl halide in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical $-NR_5R_6$ (in which R_5 represents a hydrogen atom and R_6 represents an alkyl

radical of 1 to 5 carbon atoms) and a radical -NH-Alk-NR_5R_6 or a radical -NH-Alk-$COOR_7$ (in which R_7 does not represent a hydrogen atom) from which, by a subsequent saponification, the compounds of formula I are obtained for which R_4 and/or R_3 represent a radical -NH-Alk-$COOR_7$ in which R_7 represents a hydrogen atom,

or

- are subjected to acylation in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical -NH-CO-Alk, or a radical -NH-CO-Alk-NR_9R_{10}, which are then subjected to alkylation in order to obtain a radical -N(R_{11})-CO-Alk or a radical -N(R_{11})-CO-Alk-NR_9R_{10} where R_{11} represents a radical -Alk-$COOR_{12}$ in which R_{12} does not represent a hydrogen atom, the latter compounds are then optionally subjected to saponification in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical -N(R_{11})-CO-Alk or a radical -N(R_{11})-CO-Alk-NR_9R_{10} where R_{11} represents a radical -Alk-COOH,

or

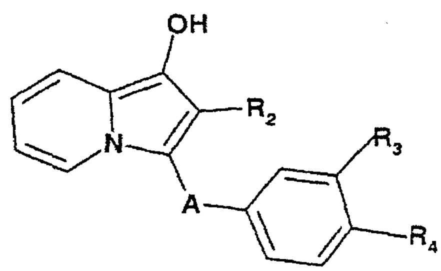
- are subjected to sulphonylation in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical $-NH-SO_2-Alk$ or a radical $-NH-SO_2-Alk-NR_9R_{10}$, which are then subjected to alkylation in order to obtain a radical $-N(R_{11})-SO_2-Alk$ or a radical $-N(R_{11})-SO_2-Alk-NR_9R_{10}$ where R_{11} represents a radical $-Alk-COOR_{12}$ in which R_{12} does not represent a hydrogen atom, the latter compounds are then optionally subjected to saponification in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical $-N(R_{11})-SO_2-Alk$ or a radical $-N(R_{11})-SO_2-Alk-NR_9R_{10}$ where R_{11} represents a radical $-Alk-COOH$

b) in that the compounds of formula Id in which R_3 and/or R_4 represent an alkoxycarbonyl radical are subjected to saponification in order to obtain the compounds of formula I in which R_3 and/or R_4 represent a carboxyl radical,

or

c) in that when R_1 represents a benzyloxy radical, the compounds of formula Ia are subjected to the action of trifluoroacetic acid or the

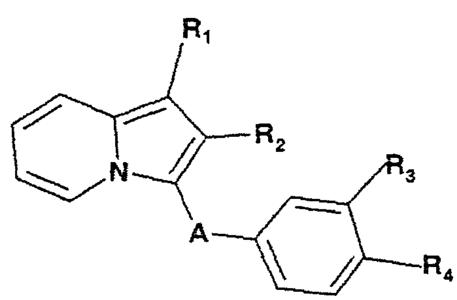
compounds of formula Id to hydrogenation, in order to obtain the compounds of formula If,



(If)

in which R_3 and/or R_4 have the meanings given above,

and then in that the compounds of formula If are subjected to O-alkylation in order to obtain the compounds of formula Ig,



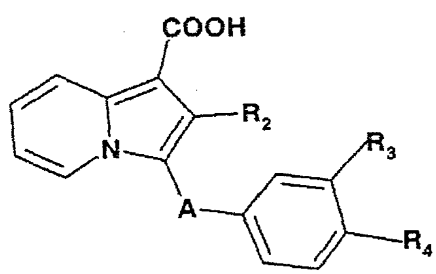
(Ig)

in which R_3 and/or R_4 have the meanings given above, and R_1 represents a linear or branched alkoxy radical of 1 to 5 carbon atoms, a radical $-O-(CH_2)_n-cAlk$, a radical $-O-Alk-COOR_7$, a radical

-O-Alk-NR_5R_6, a radical -O-$(CH_2)_n$-Ph, or a radical -O-Alk-O-R_8 – which, when R_8 represents a radical -$COCH_3$, can give, by subsequent saponification, a radical -O-Alk-OH – or a radical -O-Alk-CN which, by treatment with hydroxylamine, gives a radical -O-Alk-C(NH_2)=NOH,

or

d) in that when R_1 represents an alkoxycarbonyl radical, the compounds of formula Ia are subjected to saponification in order to obtain the compounds of formula Ih,



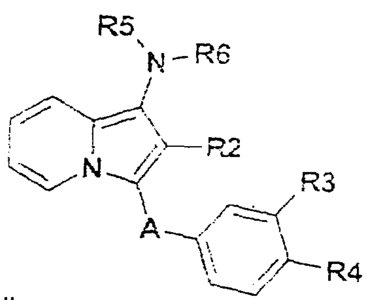
(Ih)

in which R_3 and/or R_4 have the meanings given above, which are then subjected to the action of an amine derivative in order to obtain the compounds of formula I in which R_1 represents a radical -CO-NH-Alk or a radical -CO-NH-Ph, or to the action of an amino acid derivative in order to obtain the compounds of formula I in which R_1 represents a radical -CO-NH-$(CH_2)_m$-$COOR_7$,

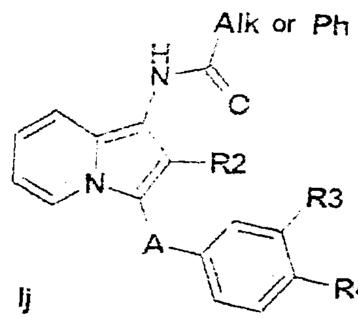
or

e) in that when R_1 represents a radical $-NH-CO_2tButyl$, the compounds of formula Ia or Id are subjected

- either to alkylation followed by deprotection and an optional second alkylation in order to obtain the compounds of formula Ii,
- or to deprotection, followed by acylation in order to obtain the compounds of formula Ij



Ii



Ij

Figures 1 and 2 represent the synthesis scheme for products Ia to Ig.

FIGURE 1

GENERAL SYNTHESIS SCHEME

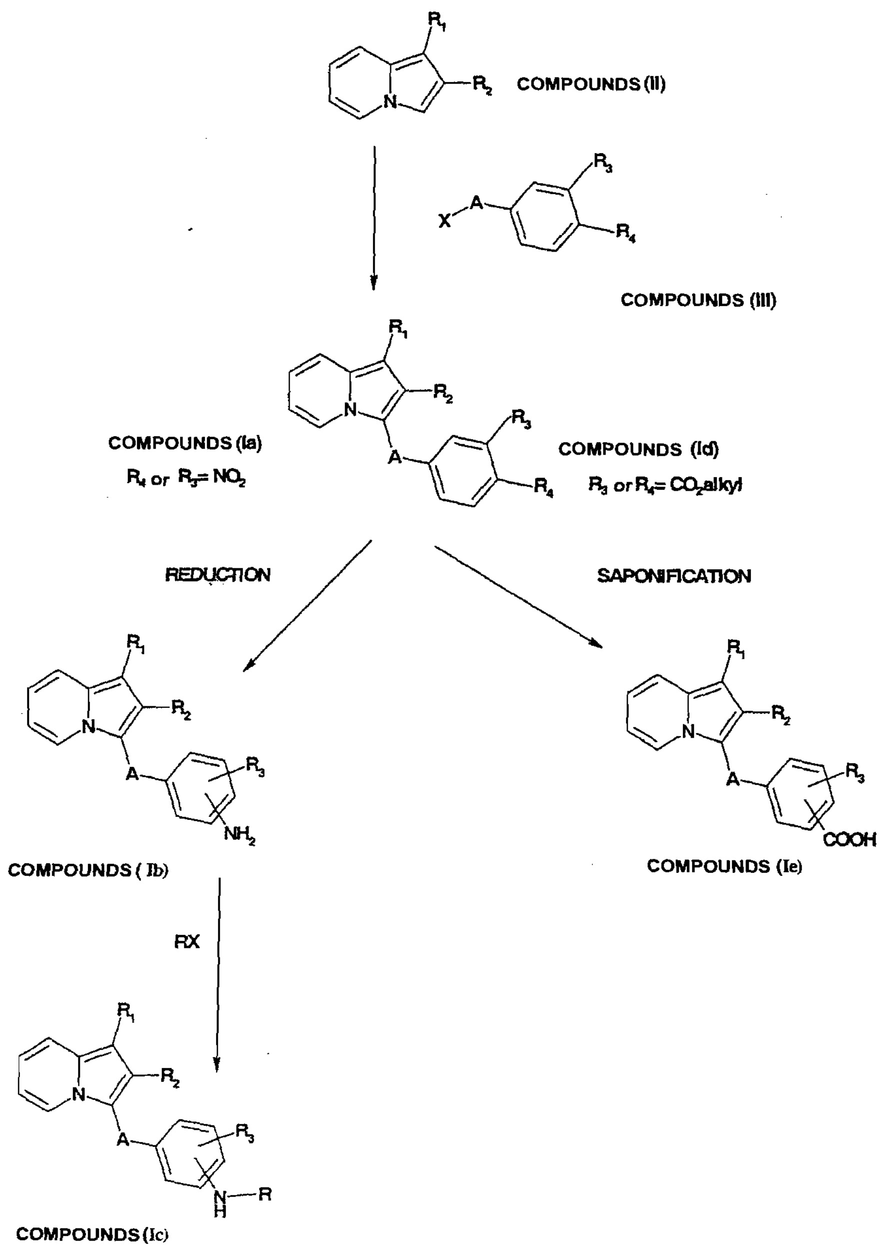
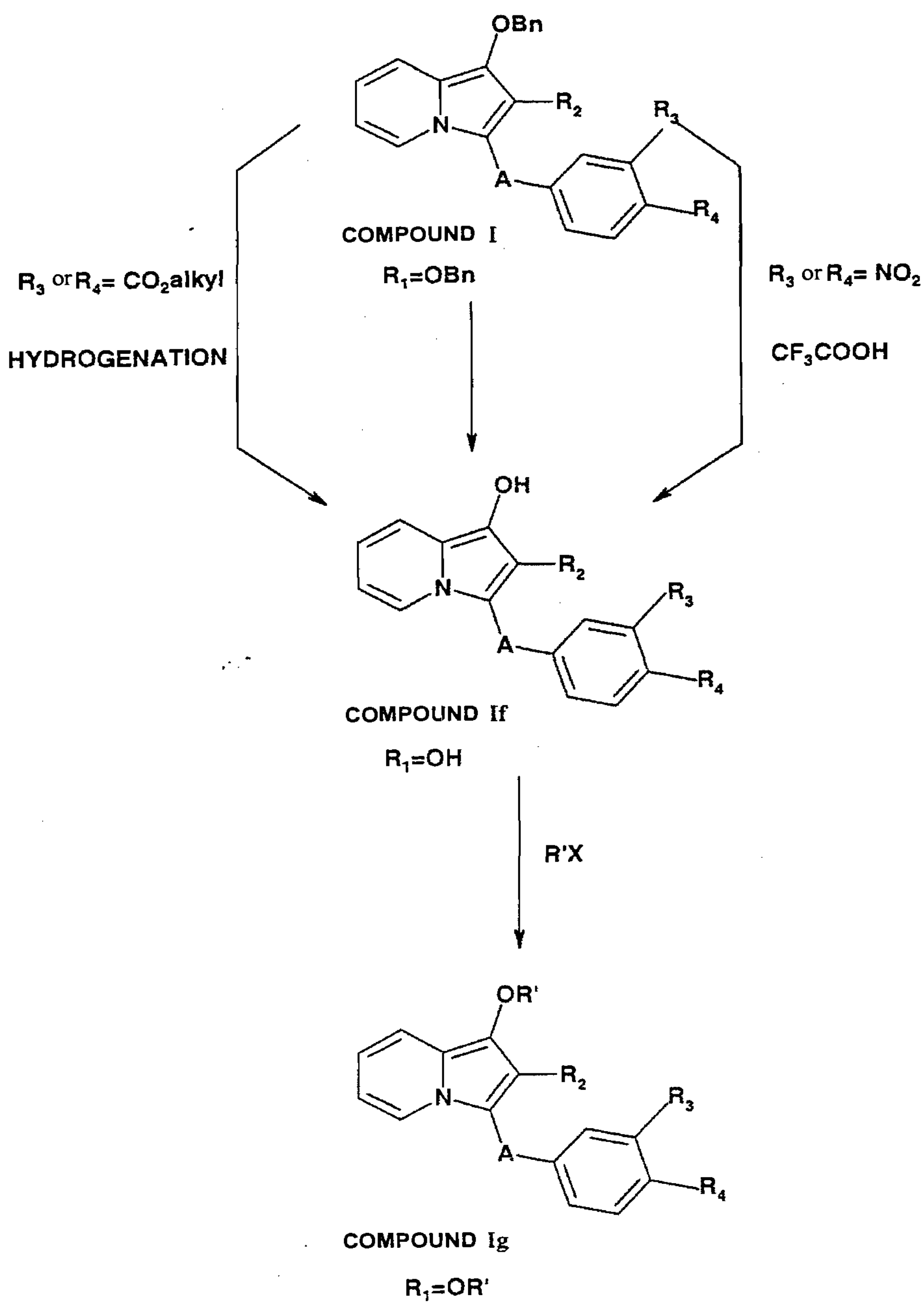


FIGURE 2


OBn
R_2
R_3
A
R_4
COMPOUND I
R_1=OBn
R_3 or R_4= CO_2alkyl
HYDROGENATION
R_3 or R_4= NO_2
CF_3COOH
OH
COMPOUND If
R_1=OH
R'X
OR'
COMPOUND Ig
R_1=OR'

The compounds according to the invention, when R_3 and/or R_4 represent a nitro radical, are prepared with known benzoylation methods (*Eur. J. Med. Chem. Chim. Ther.*, (1983), 18(4), pp. 339-346) from an indolizine derivative of formula II, and a nitrobenzoyl chloride derivative or a nitrobenzenesulphonyl chloride derivative, which compounds correspond to a compound of formula III. The compounds of formula Ia are thus obtained.

The compounds of formula Ib in which R_3 and/or R_4 represent an amino radical are obtained from the compounds of formula Ia by reducing the nitro functional group. By subjecting the compounds of formula Ib to the action of an alkyl halide, the compounds of formula Ic are obtained for which R_3 and/or R_4 represent a radical $-NR_5R_6$ (in which R_5 represents a hydrogen atom and R_6 has the meanings given above), a radical -NH-Alk-NR_5R_6 or a radical -NH-Alk-$COOR_7$ in which R_7 does not represent a hydrogen atom. The compounds for which R_7 represents a hydrogen atom are obtained from the latter compounds by subjecting them to subsequent saponification.

By acylating the compounds of formula Ib, the compounds of formula Ic are obtained for which R_3 and/or R_4 represent a radical -NH-CO-Alk or a radical -NH-CO-Alk-NR_9R_{10}.

By subjecting these compounds for which R_3 and/or R_4 represent a radical -NH-CO-Alk or a radical -NH-CO-Alk-NR_9R_{10} to alkylation with a derivative containing an alkoxycarbonyl residue, the compounds of formula I are obtained for which R_3 and/or R_4 represent a radical -N(R_{11})-CO-Alk or a radical -N(R_{11})-CO-Alk-NR_9R_{10} where R_{11} represents a radical -Alk-$COOR_{12}$ where R_{12} does not represent a hydrogen atom. By subjecting the latter products to saponification, compounds are obtained for which R_3 and/or R_4 represent a radical -N(R_{11})-CO-Alk or a radical -N(R_{11})-CO-Alk-NR_9R_{10} where R_{11} represents a radical -Alk-COOH.

By sulphonylation of the compounds of formula Ib, the compounds of formula Ic are obtained for which R_3 and/or R_4 represent a radical -NH-SO_2-Alk or a radical -NH-SO_2-Alk-NR_9R_{10}.

By subjecting these compounds for which R_3 and/or R_4 represent a radical -NH-SO_2-Alk or a radical -NH-SO_2-Alk-NR_9R_{10} to alkylation with a derivative containing an alkoxycarbonyl residue, the compounds of formula I are obtained for which R_3 and/or R_4 represent a radical -N(R_{11})-SO_2-Alk or a radical -N(R_{11})-SO_2-Alk-NR_9R_{10} where R_{11} represents a radical -Alk-$COOR_{12}$ where R_{12} does not represent a hydrogen atom. By subjecting the latter products to saponification,

compounds are obtained for which R_3 and/or R_4 represent a radical $-N(R_{11})-SO_2-Alk$ or a radical $-N(R_{11})-SO_2-Alk-NR_9R_{10}$ where R_{11} represents a radical -Alk-COOH.

By reacting an indolizine derivative of formula II with an alkoxycarbonylbenzoyl chloride derivative of formula III, the compounds of formula Id are obtained in which R_3 and/or R_4 represent an alkoxycarbonyl radical. By subjecting the latter compounds to saponification, the compounds of formula Ie are obtained in which R_3 and/or R_4 represent a carboxyl radical.

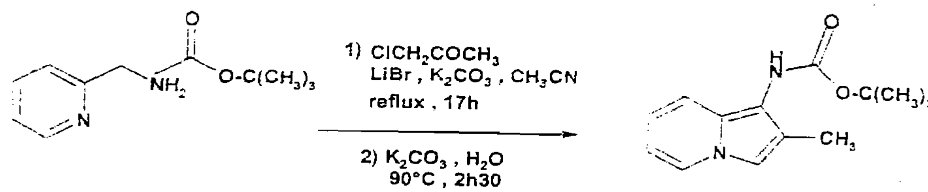
As represented in Figure 2, starting with the compounds of formula I in which R_1 represents a benzyloxy radical and R_3 or R_4 represents an alkoxycarbonyl radical, it is possible to obtain, by subjecting these compounds to hydrogenation, the compounds of formula If. When R_3 or R_4 represents a nitro radical, the compounds of formula If are obtained by the action of trifluoroacetic acid.

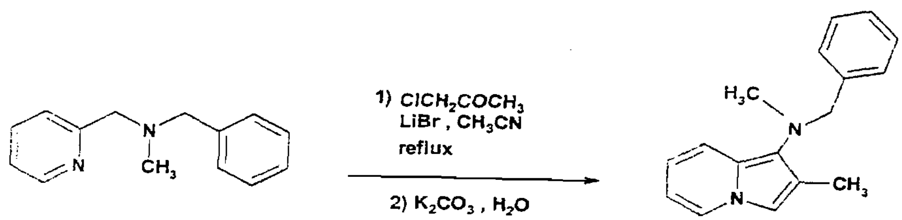
By subjecting the compounds of formula If to O-alkylation, the compounds of formula Ig are obtained in which R_1 represents a linear or branched alkoxy radical of 1 to 5 carbon atoms, a radical $-O-(CH_2)_n-cAlk$, a radical $-O-Alk-COOR_7$, a radical $-O-Alk-NR_5R_6$, a radical $-O-(CH_2)_n-Ph$, a radical

$-O-Alk-O-R_8$ – which, when R_8 represents a radical $-COCH_3$, can give, by saponification, the radical -O-Alk-OH, - a radical -O-Alk-CN which can give the radical $-O-Alk-C(NH_2):NOH$ by treating with hydroxylamine.

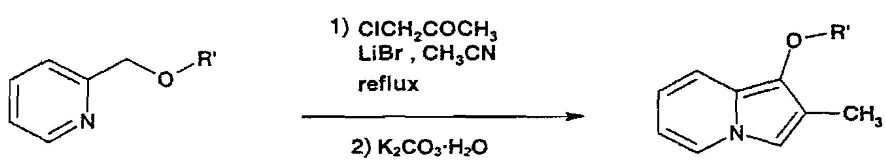
To obtain the compounds of formula Ih in which R_1 is a carboxyl radical and A is a radical -CO- or a radical $-SO_2$, the compounds of formula Ia in which R_1 is an alkoxycarbonyl radical are subjected to saponification. The indolizin-1-ylcarboxylic acid derivatives of formula Ih thus obtained can then be subjected to the action of an amine in order to prepare the compounds of formula Ih in which R_1 represents a radical -CO-NH-Alk or a radical -CO-NH-Ph, or to the action of an amino acid derivative in order to obtain the compounds of formula I in which R_1 represents a radical $-CO-NH-(CH_2)_m-COOR_7$.

The compounds of formula Ia, when R_1 represents a radical -NH-COO*t*Butyl or a radical $-N(CH_3)CH_2C_6H_5$ are prepared according to the following synthesis schemes using the Tschitschibabin reaction (*Synthesis*, (1975), p. 209) in order to prepare the indolizines.





The compounds of formula Ia, when R_1 represents a radical $-OCH_3$ or a radical $-OCH_2C_6H_5$, are also prepared using the Tschitschibabin reaction according to the following synthesis schemes:



R' = CH_3, $CH_2C_6H_5$

The compounds of formula I are potent antagonists of b-FGF. Their capacities to inhibit angiogenesis have been demonstrated *in vitro* and *in vivo*. Furthermore it has been demonstrated that the

compounds of formula I are potent selective inhibitors of b-FGF.

Angiogenesis is a process of generation of new capillary vessels. An uncontrolled proliferation of endothelial cells is observed in tumour neovascularization processes. It has been shown *in vitro* and *in vivo* that several growth factors stimulate this proliferation, FGF 2 or b-FGF being the first and the most well-characterized of these growth factors. b-FGF is a protein of 18000 D which induces proliferation, migration and protease production by endothelial cells in culture and neovascularization *in vivo*. b-FGF interacts with the endothelial cells via 2 classes of receptors, the high-affinity receptors with tyrosine kinase activity (FGFRs) and the low-affinity receptors of the heparin sulphate proteoglycan (HSPG) type situated at the surface of the cells and in the extracellular matrices. While the paracrine role of b-FGF on endothelial cells is widely described, b-FGF could also act on these cells through an autocrine process. Thus, b-FGF and its receptors represent very suitable targets for therapies aimed at inhibiting the angiogenesis process (Keshet E., Ben-Sasson S.A., *J. Clin. Invest.*, (1999), Vol. 501, pp. 104-1497; Presta M., Rusnati M., Dell'Era P., Tanghetti E.,

Urbinati C., Giuliani R. et al., *New York: Plenum Publishers*, (2000), pp. 7-34).

Moreover, systematic studies aimed at determining the expression of b-FGF and its receptors (FGFR) on various types of tumour cells demonstrate that a cellular response to b-FGF is functional in a great majority of human tumour lines studied. These results support the hypothesis that an antagonist of b-FGF could also inhibit the proliferation of tumour cells (Chandler L.A., Sosnowski B.A., Greenlees L., Aukerman S.L., Baird A., Pierce G.F., *Int. J. Cancer*, (1999), Vol. 58, pp. 81-451).

b-FGF plays an important role in the growth and maintenance of prostate cells. It has been shown, both in animal models and in humans, that an alteration of the cellular response to b-FGF plays a crucial role in the progression of prostate cancer. Indeed, in these pathologies, both an increase in the production of b-FGF by the fibroblasts and the endothelial cells present in the tumour and an increase in the expression of the FGFR receptors on tumour cells are recorded. Thus, a paracrine stimulation of prostate cancer cells occurs, and this process could be a major component of this pathology. Thus, a compound possessing an FGFR receptor antagonizing activity such as the compounds of the present invention can represent a therapy of choice

in these pathologies (Giri D., Ropiquet F., *Clin. Cancer Res.*, (1999), Vol. 71, pp. 5-1063; Doll J.A., Reiher F.K., Crawford S.E., Pins M.R., Campbell S.C., Bouck N.P., *Prostate*, (2001), Vol. 305, pp. 49-293).

Several studies show the presence of b-FGF and of its FGFR receptors both in human breast tumour lines (in particular MCF7) and in biopsies of tumours. b-FGF could be responsible, in this pathology, for the appearance of the very aggressive phenotype inducing high metastasization. Thus, a compound possessing an FGF receptor antagonizing activity, such as the compounds of formula I, may represent a therapy of choice in these pathologies (Vercoutter-Edouart A-S., Czeszak X., Crépin M., Lemoine J., Boilly B., Le Bourhis X. et al., *Exp. Cell Res.*, (2001), Vol. 262, pp. 59-68).

Cancerous melanomas are tumours which induce metastases at a high frequency and which are very resistant to various chemotherapy treatments. The angiogenesis processes play a preponderant role in the progression of a cancerous melanoma. Furthermore, it has been shown that the probability of the appearance of metastases increases very strongly with the increase in the vascularization of the primary tumour. Melanoma cells produce and secrete various angiogenic factors, including b-FGF. Thus, it has been shown that

inhibition of the cellular effect of b-FGF by soluble FGFR1 blocks *in vitro* the proliferation and the survival of melanoma tumour cells and blocks *in vivo* tumour progression. Thus, a compound possessing FGFR receptor antagonizing activity, such as the compounds of the present invention, may represent a therapy of choice in these pathologies (Rofstad E.K., Halsor E.F., *Cancer Res.*, (2000); Yayon A., Ma Y-S., Safran M., Klagsbrun M., Halaban R., *Oncogene*, (1997), Vol. 14, pp. 2999-3009).

Glioma cells produce *in vitro* and *in vivo* b-FGF and possess various FGFRs at their surface. This therefore suggests that b-FGF, through an autocrine and paracrine effect, plays a pivotal role in the progression of this type of tumour. Furthermore, like the majority of solid tumours, the progression of gliomas and their capacity to induce metastases is highly dependent on the angiogenic processes in the primary tumour. It has thus been shown that FGFR1 antisenses block the proliferation of human astrocytomas. Furthermore, molecules of the naphthalenesulphonate family are described for inhibiting the cellular effects of b-FGF *in vitro* and the angiogenesis induced by these growth factors *in vivo*. Intracerebral injection of these compounds induces a very significant increase in apoptosis, a

substantial decrease in angiogenesis resulting in considerable regression of gliomas in rats. Thus, a compound possessing an antagonist activity for b-FGF and the FGFR receptors, such as the compounds of the present invention, may represent a therapy of choice in these pathologies (Yamada S.M., Yamaguchi F., Brown R., Berger M.S., Morrison R.S., *Glia*, (1999), Vol. 76, pp. 28-66; Auguste P., Gürsel D.B., Lemière S., Reimers D., Cuevas P., Carceller F., et al., *Cancer Res.*, (2001), Vol. 26, pp. 61-1717).

More recently, the potential role of proangiogenic agents in leukaemias and lymphomas has been documented. Indeed, it has been reported, in general, that cellular clones in these pathologies may be either naturally destroyed by the immune system or switch to an angiogenic phenotype which promotes their survival and then their proliferation. This change of phenotype is induced by an overexpression of angiogenic factors, in particular by the macrophages, and/or mobilization of these factors from the extracellular matrix (Thomas D.A., Giles F.J., Cortes J., Albitar M., Kantarjian H.M., *Acta Haematol*, (2001), Vol. 207, pp. 106-190). Among the angiogenic factors, b-FGF has been detected in numerous lymphoblastic and hematopoietic tumour cell lines. The FGFR receptors are also present on a majority of these lines, suggesting a

possible autocrine cellular effect of b-FGF inducing the proliferation of these cells. Moreover, it has been reported that bone marrow angiogenesis by paracrine effects was correlated with the progression of some of these pathologies.

More particularly, it has been shown, in CLL (chronic lymphocytic leukaemia) cells that b-FGF induces an increase in the expression of the antiapoptotic protein (Bcl2) leading to an increase in the survival of these cells and therefore greatly participates in their cancerization. Furthermore, the b-FGF levels measured in these cells are very well correlated with the stage of clinical advance of the disease and the resistance to the chemotherapy applied in this pathology (fludarabine). Thus, a compound possessing an FGFR receptor antagonizing activity, such as the compounds of the present invention, may represent a therapy of choice, either in combination with fludarabine or other active products, in this pathology (Thomas D.A., Giles F.J., Cortes J., Albitar M., Kantarjian H.M., *Acta Haematol*, (2001), Vol. 207, pp. 106-190; Gabrilove J.L. *Oncologist*, (2001), Vol. 6, pp. 4-7).

A correlation exists between the process of bone marrow angiogenesis and the extramedullary diseases in CML (chronic myelomonocytic leukaemia).

Various studies demonstrate that the inhibition of angiogenesis, in particular by a compound possessing an FGFR receptor antagonizing activity could represent a therapy of choice in this pathology.

The proliferation and the migration of vascular smooth muscle cells contribute to intimal hypertrophy of the arteries and thus plays a preponderant role in atherosclerosis and in restenosis following angioplasty and endarterectomy.

Studies *in vivo* show, after lesion of the carotid by balloon injury, a local production of b-FGF. In this same model, an anti-FGF2 neutralizing antibody inhibits the proliferation of vascular smooth muscle cells and thus decreases intimal hypertrophy.

A chimeric protein FGF2 bound to a molecule such as saponin blocks the binding of b-FGF to its FGFR receptors, inhibits the proliferation of vascular smooth muscle cells *in vitro* and intimal hypertrophy *in vivo* (Epstein C.E., Siegall C.B., Biro S., Fu Y.M., FitzGerald D., *Circulation*, (1991), Vol. 87, pp. 84-778; Waltenberger J., *Circulation*, (1997), pp. 96-4083).

Thus, antagonists of the FGFR receptors, such as the compounds of the present invention, represent a therapy of choice, either alone or in combination with antagonist compounds for other growth factors involved

in these pathologies, such as PDGF, in the treatment of pathologies linked to the proliferation of vascular smooth muscle cells such as atherosclerosis, restenosis post-angioplasty or following the fitting of endovascular prostheses (stents) or during aorto-coronary artery by-pass surgery.

Cardiac hypertrophy occurs in response to a stress of the ventricular wall induced by an overload in terms of pressure or volume. This overload may be the consequence of numerous physiopathological states such as hypertension, AC (aortic coarctation), myocardial infarction and various vascular disorders. The consequences of this pathology are morphological, molecular and functional changes such as hypertrophy of cardiac myocytes, the accumulation of matrix proteins and the re-expression of foetal genes. b-FGF is involved in this pathology. Indeed, the addition of b-FGF to cultures of cardiomyocytes of newborn rats modifies the profile of the corresponding genes to contractile proteins leading to a foetal-type gene profile. Additionally, adult rat myocytes show a hypertrophic response under the effect of b-FGF, this response being blocked by anti-b-FGF neutralizing antibodies. Experiments carried out *in vivo* on transgenic knockout mice for b-FGF show that b-FGF is the major stimulating factor for cardiac myocyte

hypertrophy in this pathology (Schultz JeJ., Witt S.A., Nieman M.L., Reiser P.J., Engle S.J., Zhou M. et al., *J. Clin. Invest.*, (1999), Vol. 19, pp. 104-709).

Accordingly, a compound, such as the compounds of the present invention, possessing FGFR receptor antagonizing activity represents a therapy of choice in the treatment of cardiac insufficiency and any other pathology associated with a degeneracy of the cardiac tissue. This treatment could be carried out alone or in combination with current treatments (beta-blockers, diuretics, angiotensin antagonists, antiarrhythmics, anti-calcium agents, antithrombotics, and the like).

Vascular disorders caused by diabetes are characterized by an alteration of vascular reactivity and of blood flow, hyperpermeability, an exacerbated proliferative response and an increase in matrix protein deposits. More precisely, b-FGF is present in the preretinal membranes of patients with diabetic retinopathies, in the membranes of underlying capillaries and in the vitreous humour of patients suffering from proliferative retinopathies. A soluble FGF receptor capable of binding b-FGF is developed in vascular disorders linked to diabetes (Tilton R.G., Dixon R.A.F., Brock T.A., *Exp. Opin. Invest. Drugs*, (1997), Vol. 84, pp. 6-1671). Thus, a compound such as

the compounds of formula I possessing an FGFR receptor antagonizing activity represents a therapy of choice either alone or in combination with antagonist compounds for other growth factors involved in these pathologies, such as VEGF.

Rheumatoid arthritis (RA) is a chronic disease with an unknown aetiology. While it affects numerous organs, the most severe form of RA is a progressive synovial inflammation of the joints leading to destruction. Angiogenesis appears to greatly affect the progression of this pathology. Thus, b-FGF has been detected in the synovial tissue and in the joint fluid of patients suffering from RA, indicating that this growth factor is involved in the initiation and/or progression of this pathology. In AIA models (adjuvant-induced model of arthritis) in rats, it has been shown that the overexpression of b-FGF increases the severity of the disease whereas an anti-b-FGF neutralizing antibody blocks the progression of RA (Yamashita A., Yonemitsu Y., Okano S., Nakagawa K., Nakashima Y., Irisa T. et al., *J. Immunol.*, (2002), Vol. 57, pp. 168-450; Manabe N., Oda H., Nakamura K., Kuga Y., Uchida S., Kawaguchi H., *Rheumatol*, (1999), Vol. 20, pp. 38-714). Thus, the compounds according to the invention represent a therapy of choice in this pathology.

IBDs (inflammatory bowel diseases) comprise two forms of chronic inflammatory diseases of the intestine: UC (ulcerative colitis) and Crohn's disease (CD). IBDs are characterized by an immune dysfunction which results in an inappropriate production of inflammatory cytokines inducing the establishment of a local microvascular system. The consequence of this angiogenesis of inflammatory origin is an intestinal ischaemia induced by vasoconstriction. High circulating and local levels of b-FGF were measured in patients suffering from these pathologies (Kanazawa S., Tsunoda T., Onuma E., Majima T., Kagiyama M., Kkuchi K., *American Journal of Gastroenterology*, (2001), Vol. 28, pp. 96-822; Thorn M., Raab Y., Larsson A., Gerdin B., Hallgren R., *Scandinavian Journal of Gastroenterology*, (2000), Vol. 12, pp. 35-408). The compounds of the invention which exhibit a high antiangiogenic activity in a model of inflammatory angiogenesis represent a therapy of choice in these pathologies.

FGFR1, 2 and 3 are involved in the processes of chronogenesis and osteogenesis. Mutations leading to the expression of permanently activated FGFRs have been linked to a large number of human genetic diseases which result in malformations of the skeleton, such as Pfeiffer, Crouzon, Apert, Jackson-Weiss and Beare-

Stevenson cutis gyrata syndromes. Some of these mutations, which affect more particularly FGFR3, lead in particular to achondroplasia (ACH), hypochondroplasia (HCH) and TD (Thanatophoric dysplasia), ACH being the most common form of nanism. From a biochemical point of view, sustained activation of these receptors occurs through dimerization of the receptor in the absence of ligand (Chen. L., Adar R., Yang X., Monsonego E.O., LI C., Hauschka P.V., Yagon A. and Deng C.X., (1999), *The Journal of Clin. Invest.*, Vol. 104, No. 11, pp. 1517-1525). Thus, the compounds of the invention which exhibit an antagonist activity on the binding of b-FGF and FGFR and which thus inhibit the dimerization of the receptor represent a therapy of choice in these pathologies.

By virtue of their low toxicity and their pharmacological and biological properties, the compounds of the present invention find application in the treatment of any carcinoma having a high degree of vascularization (lung, breast, prostate, oesophagus) or inducing metastases (colon, stomach, melanoma) or sensitive to b-FGF in an autocrine manner or, finally, in lymphoma and leukaemia type pathologies. These compounds represent a therapy of choice either alone or in combination with an appropriate chemotherapy. The compounds according to the invention also find

application in the treatment of cardiovascular diseases such as atherosclerosis, post-angioplasty restenosis, in the treatment of diseases linked to the complications which appear following the fitting of endovascular prostheses and/or aorto-coronary artery by-passes or other vascular transplants and cardiac hypertrophy or vascular complications of diabetes such as diabetic retinopathies. The compounds according to the invention also find application in the treatment of chronic inflammatory diseases such as rheumatoid arthritis or IBDs. Finally, the compounds according to the invention may be used in the treatment of achondroplasia (ACH), hypochondroplasia (HCH) and TD (thanatrophoric dysplasia).

According to another of its features, the subject of the present invention is therefore a pharmaceutical composition containing, as active ingredient, a compound of formula I according to the invention or one of its pharmaceutically acceptable salts, optionally in combination with one or more inert and appropriate excipients.

The said excipients are chosen according to the pharmaceutical dosage form and the desired mode of administration: oral, sublingual, subcutaneous, intramuscular, intravenous, transdermal, transmucosal, local or rectal.

The pharmaceutical compositions according to the present invention are administered by the oral route.

In the pharmaceutical compositions of the present invention for oral administration, the active ingredients may be administered in a unit form for administration, as a mixture with conventional pharmaceutical carriers. The appropriate unit forms for administration comprise, for example, tablets, which are optionally scored, gelatine capsules, powders, granules and oral solutions or suspensions.

When a solid composition in the form of tablets is prepared, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatine, starch, lactose, magnesium stearate, talc, gum arabic and the like. It is possible to coat the tablets with sucrose or other appropriate materials, or alternatively it is possible to treat them so that they have a prolonged or delayed activity and they continuously release a predetermined quantity of active ingredient.

A preparation in the form of gelatine capsules is obtained by mixing the active ingredient with a diluent and pouring the mixture obtained in soft or hard gelatine capsules.

A preparation in syrup or elixir form may contain the active ingredient together with a sweetener, preferably calorie-free, methylparaben and propylparaben as antiseptics, a taste enhancer and an appropriate colouring.

Water-dispersible powders or granules may contain the active ingredient as a mixture with dispersing agents, wetting agents or suspending agents, such as polyvinylpyrrolidone, and with sweeteners or flavour corrigents.

The active ingredient may also be formulated in the form of microcapsules, optionally with one or more carriers or additives.

In the pharmaceutical compositions according to the present invention, the active ingredient may also be in the form of an inclusion complex in cyclodextrins, their ethers or their esters.

The quantity of active ingredient to be administered depends, as always, on the degree of progression of the disease and the age and weight of the patient.

The compositions according to the invention, for oral administration, therefore contain recommended doses of 0.01 to 700 mg.

The following examples, given without limitation, illustrate the present invention.

Preparation I

Synthesis of *tert*-butyl 2-methylindolizin-1-ylcarbamate

11.7 g (62.4 mmol) of potassium carbonate and 6.3 g of (72 mmol) of lithium bromide are added to 10 g (48 mmol) of tert-butyl [(pyridin-2-yl)methyl]carbamate in 50 ml of acetonitrile, followed by 5 ml (62.4 mmol) of chloroacetone, and the medium is heated under reflux overnight.

It is cooled and 40 ml of water and 11.7 g (62.4 mmol) of potassium carbonate are added, and the medium is heated at 90°C for 2 h 30 min. The reaction medium is cooled and extracted with ethyl acetate.

The organic phase is removed after settling out, washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure. The product is purified by flash chromatography on a silica column, eluting with a toluene/ethyl acetate (95:5) mixture. 6.27 g of a white powder are collected.

Yield: 53%

Melting point: 111°C

Preparation II

Synthesis of *N*-benzyl-*N*-methyl-*N*-(2-methylindolizin-1-yl)amine

This compound is obtained according to the same procedure as the compound of Preparation I, using the Tschitschibabin reaction and starting with 2.47 g of *N*-benzyl-*N*-methyl-*N*-[(pyridin-2-yl)methyl]amine and chloroacetone. 970 mg of a yellow oil are obtained.

Yield: 34%

Mass spectrometry (ES+ mode): MH+ = 251

Preparation III

Synthesis of 1-methoxy-2-methylindolizine

This compound is obtained starting with 2-(methoxymethyl)pyridine and chloroacetone, using the Tschitschibabin reaction. The product is isolated in the form of a yellow oil which crystallizes in the freezer.

Yield: 77.5%

Mass spectrometry (ES+ mode): MH+ = 161.8

Preparation IV

Synthesis of 1-benzyloxy-2-methylindolizine

This compound is obtained according to the same procedure as that desribed in Preparation I using the Tschitschibabin reaction.

The product is isolated in the form of a yellow oil.

Yield: 39%

Example 1

(1-Methoxy-2-methylindolizin-3-yl)(3-methoxy-4-nitrophenyl)methanone

4.21 g (0.0195 mol) of 3-methoxy-4-nitrobenzoyl chloride are added to 3 g (0.0186 mol) of 1-methoxy-2-methylindolizine whose preparation is described in Preparation III, dissolved in 50 ml of 1,2-dichloroethane, and the medium is stirred at room temperature for 4 hours.

The reaction medium is poured over water. The organic phase is separated after settling out, washed with an aqueous sodium bicarbonate solution and then with water, dried over sodium sulphate and concentrated under vacuum.

The residue is purified by chromatography on a silica column, eluting with dichloromethane. After evaporation, 6.05 g of a yellow solid are obtained.

Yield: 95%

Melting point: 287°C

Examples 2 to 18

By carrying out the procedure according to the preparation described above, the compounds which are described in Table I below, are synthesized by benzoylation of the 3-position of the indolizines

variously substituted at the 1- and 2-positions with suitably substituted benzoyl chlorides.

TABLE I

Ex-ample	**R_1**	**R_2**	**R_3**	**R_4**	**Yield (%)**	**Melting point (°C) or mass spectrometry (MH+)**
2	OBn	Ph	OMe	NO_2	94	186°C
3	OBn	Me	OMe	NO_2	95	153°C
4	OBn	Me	H	CO_2Me	70.5	110°C
5	OMe	cPr	OMe	NO_2	81	112°C
6	OMe	Ph	OMe	NO_2	82	65°C
7	OMe	Me	H	NO_2	88	146°C
8	OMe	Me	H	CO_2Me	92	143°C
9	OMe	Me	CO_2Me	H	75	121°C
10	OMe	Me	NO_2	CO_2Me	57	138°C
11	OMe	Me	OMe	CO_2Me	88.5	145°C
12	OMe	Me	H	CH_2CO_2Me	75	94°C
13	CO_2Et	Me	OMe	-NO_2	91	137°C
14	CO_2Et	Me	OMe	CO_2Me	45.5	141°C
15	CO_2Et	Ph	OMe	NO_2	85	151°C
16	CO_2Et	Me	H	CO_2Me	98	139°C
17	N(Me)Bn	Me	OMe	NO_2	90	MH+ = 430.3
18	NHBOC	Me	OMe	NO_2	76	MH+ = 426.5

Bn = benzyl

Me = methyl

Et = ethyl

BOC = *t*butoxycarbonyl

Example 19

(1-Amino-2-methylindolizin-3-yl)(3-methoxy-4-nitrophenyl)methanone

2.32 ml of trifluoroacetic acid are added dropwise to a solution of 643 mg (1.51 mmol) of *tert*-butyl 3-(3-methoxy-4-nitrobenzoyl)-2-methylindolizin-1-ylcarbamate in 20 ml of dichloromethane, cooled to 0°C. Once the introduction is complete, the medium is allowed to return to room temperature and it is stirred for 4 hours. The reaction medium is poured over a saturated aqueous potassium carbonate solution and extracted with ethyl acetate. The organic phase is separated after settling out, washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure. The crystals obtained are taken up in isopropyl ether, filtered off, washed with isopropyl ether and then dried. 425 mg of a brown solid are obtained.

Yield: 87%

Mass spectrometry (ES+ mode) MH^+ = 326.3

Example 20

***N*-[3-(3-Methoxy-4-nitrobenzoyl)-2-methylindolizin-1-yl]methanesulphonamide**

0.292 ml (3.78 mmol) of mesyl chloride is added to a solution of 350 mg (1.08 mmol) of the compound of Example 19 in 3 ml of pyridine, and the medium is stirred at room temperature for 4 hours. The reaction medium is concentrated under reduced pressure.

The residue is taken up in 1 N hydrochloric acid and extracted with dichloromethane. The organic phase is separated after settling out, washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure. The residue is crystallized from ethanol. 327 mg of yellow crystals are obtained.

Yield: 75%

Mass spectrometry (ES+ mode) MH^+ = 404.3

Example 21

(3-Methoxy-4-nitrophenyl)[2-methyl-1-(methylamino)indolizin-3-yl]methanone

Step A

Synthesis of ***tert*-butyl 3-(3-methoxy-4-nitrobenzoyl)-2-methylindolizin-1-yl(methyl)carbamate**

3.05 g (7.2 mmol) of *tert*-butyl 3-(3-methoxy-4-nitrobenzoyl)-2-methylindolizin-1-ylcarbamate in solution in 50 ml of tetrahydrofuran are added dropwise to 315 mg (7.9 mmol) of sodium hydride (at 60% as a dispersion in oil) in suspension in 10 ml of tetrahydrofuran, cooled to 0°C. After stirring for 1 hour at 0°C, 0.59 ml (9.5 mmol) of methyl iodide is added while the medium is maintained at 0°C. It is allowed to return to room temperature and it is stirred for 1 hour. The reaction medium is poured over a

saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic phase is separated after settling out, washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure. 3.47 g of an orange-coloured foam are obtained.

Yield: 96%

Mass spectrometry (ES+ mode) MH^+ = 440.3

Step B

13 ml of trifluoroacetic acid are added dropwise to a solution of 3.38 g (7.7 mmol) of the product obtained in Step A in 60 ml of dichloromethane, cooled to 0°C. When the introduction is complete, the medium is allowed to return to room temperature and it is stirred for 3 hours.

The reaction medium is poured over a saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic phase is separated after settling out, washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure.

The residue is purified by flash chromatography on a silica column, eluting with a toluene/ethyl acetate (9/1) mixture. After evaporation, 2.2 g of a red powder are obtained.

Yield: 76%

Mass spectrometry (ES+ mode) MH^+ = 340.2

Example 22

[1-(Dimethylamino)-2-methylindolizin-3-yl](3-methoxy-4-nitrophenyl)methanone

382 mg (1.1 mmol) of the compound of Example 21 in solution in 10 ml of tetrahydrofuran are added dropwise to 44 mg (1.1 mmol) of sodium hydride (at 60% in a dispersion in oil) in suspension in 5 ml of tetrahydrofuran, cooled to 0°C. Once the introduction is complete, the medium is allowed to return to room temperature over 1 hour, and then 69 µl (1.1 mmol) of methyl iodide are added and the medium is stirred at room temperature for 17 hours. The reaction medium is poured over a saturated aqueous sodium chloride solution and extracted with ethyl acetate. The organic phase is separated after settling out, washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure. The residue is purified by chromatography on a silica column, eluting with a toluene/ethyl acetate (95/5) mixture. 143 mg of an orange-coloured foam are obtained.

Yield: 37%

Example 23

(1-Hydroxy-2-methylindolizin-3-yl)(3-methoxy-4-nitrophenyl)methanone

A solution of 5 g (12 mmol) of [1-(benzyloxy-2-methylindolizin-3-yl](3-methoxy-4-nitrophenyl)methanone, a compound of Example 3, in 30 ml of trifluoroacetic acid, is heated under reflux for 2 hours.

The reaction medium is evaporated under reduced pressure. The residue is taken up in ethyl acetate, washed with an aqueous sodium bicarbonate solution and with water, and then the organic phase is dried over sodium sulphate and evaporated under reduced pressure.

The product obtained is purified by chromatography on a silica column, eluting with a dichloromethane/methanol (99/1) mixture. 2.93 g of an orange-coloured powder are obtained.

Yield: 75%

Melting point: 193°C

Example 24

Methyl 4-({[3-(3-methoxy-4-nitrobenzoyl)-2-methylindolizin-1-yl]oxy}methyl)benzoate

812 mg (3.37 mmol) of methyl 4-(bromomethyl)benzoate are added to a solution of 1 g

(3.06 mmol) of (1-hydroxy-2-methyl-3-indolizinyl)(3-methoxy-4-nitrophenyl)methanone in 16 ml of dimethylformamide, in the presence of 508 mg (3.68 mmol) of potassium carbonate, and the medium is heated at 90°C for 4 hours.

The reaction medium is poured over water and extracted with ethyl acetate.

The organic phase is washed with water, dried over sodium sulphate and evaporated to dryness. The product obtained is purified by chromatography on a silica column, eluting with a toluene/ethyl acetate (9/1) mixture. 880 mg of a yellow powder are obtained.

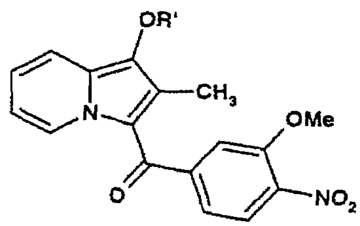
Yield: 60.5%

Melting point: 154°C

Examples 25 to 39

By carrying out the procedure according to the method described in Example 24, the compounds described in Table II below are synthesized by alkylating (1-hydroxy-2-methylindolizin-3-yl)(3-methoxy-4-nitrophenyl)methanone with appropriately chosen halogenated derivatives. To obtain the compound of Example 36, the compound of Example 35 is subjected to saponification.

TABLE II



$R_1 = OR'$

Compounds of formula Ia

Example	R′	Yield (%)	Melting point
25	$CH_2C_6H_5$-2Cl	90	173°C
26	$CH_2C_6H_5$-3Cl	74	179°C
27	$CH_2C_6H_5$-4Cl	82	162°C
28	$CH_2C_6H_5$-2OMe	84	148°C
29	$CH_2C_6H_5$-3OMe	67.5	145°C
30	$CH_2C_6H_5$-4OMe	71	135°C
31	$CH_2C_6H_5$-3CO_2Me	57	171°C
32	CH_2CO_2Et	91	127°C
33	CH_2CONH_2	65	222°C
34	$(CH_2)_2NMe_2$	26	108°C
35	$(CH_2)_2OAc$	68	Oil
36	$(CH_2)_2OH$	90	142°C
37	CH_2CN	91.5	176°C
38	iPr	19	283°C
39	CH_2cPr	22	111°C

Example 40

Methyl 4-[(1-hydroxy-2-methylindolizin-3-yl)carbonyl]benzoate

8.75 ml (86.37 mmol) of cyclohexene are added to 3.45 g (8.64 mmol) of methyl 4-[(1-(benzyloxy)-2-methylindolizin-3-yl)carbonyl]benzoate in 40 ml of ethanol, in the presence of 690 mg of 10% Pd/C, and the medium is heated under reflux for one hour.

The reaction medium is cooled to room temperature and the catalyst is removed by filtration on talc. The filtrate is under reduced pressure.

The product obtained is purified by chromatography on a silica column, eluting with a dichloromethane/methanol (98/2) mixture. 2.5 g of an orange-coloured powder are obtained.

Yield: 93.5%

Melting point: 192°C

Example 41

Methyl 4-{[1-(2-ethoxy-2-oxoethoxy)-2-methylindolizin-3-yl]carbonyl}benzoate

202 µl (1.78 mmol) of ethyl bromoacetate are added to 500 mg (1.62 mmol) of methyl 4-[(1-hydroxy-2-methylindolizin-3-yl)carbonyl]benzoate, a compound of Example 40, in 10 ml of dimethylformamide, in the

presence of 268 mg (1.94 mmol) of potassium carbonate, and the medium is heated at 90°C for one hour.

The reaction medium is cooled, poured over water and extracted with ethyl acetate, and then separated after settling out. The organic phase is washed with water, dried over sodium sulphate and evaporated under reduced pressure. The product obtained is purified by chromatography on a silica column, eluting with a toluene/ethyl acetate (9/1) mixture. 570 mg of a yellow powder are obtained.

Yield: 89%

Melting point: 84.5°C

__Example 42__

Methyl 4-({1-[(3-methoxybenzyl)oxy]-2-methylindolizin-3-yl}carbonyl)benzoate

This compound is obtained according to the same procedure as that of Example 41, by O-alkylation of methyl 4-[(1-hydroxy-2-methylindolizin-3-yl)carbonyl]benzoate with 3-methoxybenzyl bromide. A yellow powder is obtained which melts at 106°C.

Yield: 76%

__Example 43__

3-(3-Methoxy-4-nitrobenzoyl)-2-methylindolizin-1-ylcarboxylic acid

26.2 ml of 1 N sodium hydroxide are added to 5 g (13.1 mmol) of ethyl 3-(3-methoxy-4-nitrobenzoyl)-2-methylindolizin-1-ylcarboxylate, a compound of Example 13 - prepared according to the procedure of Example 1 by benzoylation of ethyl (2-methylindolizin-1-yl)carboxylate described in *J. Chem. Soc.*, (1963), pp. 3277-3280 -, in suspension in 50 ml of dioxane, and the medium is heated under reflux for 17 hours. The reaction medium is concentrated under reduced pressure. The residue is taken up in water, washed with ethyl ether, and the medium is separated after settling out. The aqueous phase is acidified to pH 6 with a potassium hydrogen sulphate solution and extracted with ethyl acetate. The organic phase is washed with water, dried over sodium sulphate and concentrated under reduced pressure. 4.9 g of an orange-coloured powder are obtained.

Yield: quantitative

Melting point: 215°C

Example 44

***N*-Ethyl 3-(3-methoxy-4-nitrobenzoyl)-2-methylindolizin-1-ylcarboxamide**

0.61 ml (4.34 mmol) of triethylamine is added to a solution of 750 mg (2.12 mmol) of the acid of Example 43 in 12 ml of dimethylformamide, followed, in

portions, by 983 mg (2.22 mmol) of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate. The medium is stirred for 5 min at room temperature and then 182 mg (2.22 mmol) of ethylamine hydrochloride are added. The reaction medium is stirred overnight at room temperature, poured over water and extracted with ethyl acetate. The organic phase is separated after settling out, washed with water, dried over sodium sulphate and concentrated under reduced pressure. The product is purified by chromatography on a silica column, eluting with dichloromethane/methanol (98/2). 700 mg of a yellow powder are obtained.

Yield: 87%

Melting point: 188°C

Example 45

Ethyl 2-({[3-(3-methoxy-4-nitrobenzoyl)-2-methylindolizin-1-yl]carbonyl}amino)acetate

This compound is obtained according to the same method as the preceding compound, by coupling 3-(3-methoxy-4-nitrobenzoyl)-2-methylindolizin-1-ylcarboxylic acid with ethyl glycinate hydrochloride. The product is purified by chromatography on a silica column, eluting with dichloromethane/methanol (93/7). A yellow powder is obtained.

Yield: 86%

Melting point: 191°C

Example 46

1-Methoxy-2-methyl-3-[(4-nitrophenyl)sulphonyl]indolizine

690 mg (3.1 mmol) of 4-nitrobenzenesulphonyl chloride in solution in 4 ml of 1,2-dichloroethane are added to 500 mg (3.1 mmol) of 1-methoxy-2-methylindolizine dissolved in 8 ml of 1,2-dichloroethane, and the medium is stirred at room temperature for 20 hours. The reaction medium is poured over water and dichloromethane. The organic phase is separated after settling out, washed with water, dried over sodium sulphate and concentrated under reduced pressure. The product is purified by chromatography on a silica column, eluting with cyclohexane/ethyl acetate (9/1). 330 mg of a yellow oil are obtained.

Yield: 31%

Example 47

Sodium salt of 4-[(1-methoxy-2-methylindolizin-3-yl)sulphonyl]benzoic acid

This compound is obtained according to the same procedure as the compound of Example 46, by sulphonylation of 1-methoxy-2-methylindolizine with 4-

chlorosulphonylbenzoic acid. The product is purified by flash chromatography on a silica column, eluting with dichloromethane/acetone (9/1). 120 mg of a yellow powder are obtained.

Yield: 11%

The product, dissolved in methanol, is salified by adding one equivalent of 1 N sodium hydroxide. The methanol is evaporated off and the residue is crystallized from acetone. The product is filtered, washed with acetone and then with ethyl ether and dried. 100 mg of sodium salt are obtained in the form of a yellow powder.

Melting point: 175°C

Example 48

(4-Amino-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone

700 mg of 10% Pd/C are added to 6 g (0.0176 mol) of (1-methoxy-2-methyl-3-indolizinyl)(3-methoxy-4-nitrophenyl)methanone, a compound of Example 1, in 100 ml of ethanol, followed by 35.71 ml (0.352 mol) of cyclohexene, and the medium is heated under reflux for 2 hours. The reaction medium is cooled, filtered over talc and the catalyst is washed with dichloromethane. The filtrate is concentrated under reduced pressure. The residue is taken up in

dichloromethane. The organic phase is washed with 1 N sodium hydroxide and then with water, dried over sodium sulphate and concentrated under reduced pressure.
5.05 g of a yellow powder are recovered. The product is salified by dissolving the powder obtained above in 60 ml of dichloromethane plus 20 ml of methanol, and then adding 21 ml of 1 N hydrochloric acid in ethyl ether. After adding ethyl ether, the precipitate obtained is filtered off, washed with ethyl ether and then dried. 5.4 g of a yellow powder in hydrochloride form are recovered.
Yield: 88%
Melting point: 198°C

Examples 49 to 57

By carrying out the procedure according to the preparation described above, the compounds described in Table III below are synthesized by reducing the nitro functional group of the compounds of formula Ia with cyclohexene in the presence of 10% Pd/C as catalyst.

TABLE III

Example	R_1	R_2	R_3	R_4	Yield (%)	Salts	Melting point or mass spectro. (MH+)
49	OMe	C_6H_5	OMe	NH_2	90	HCl, $0.45H_2O$	209°C
50	OMe	cPr	OMe	NH_2	95	HCl, $0.15H_2O$	191°C
51	CO_2Et	Me	OMe	NH_2	91	HCl	194°C
52	OCH_2CO_2Et	Me	OMe	NH_2	99	HCl	182°C
53	OCH_2CONH_2	Me	OMe	NH_2	87	HCl	MH^+=354.1
54	$O(CH_2)_2OH$	Me	OMe	NH_2	89	HCl, $0.5H_2O$	205°C
55	OMe	Me	H	NH_2	86	HCl, $0.2H_2O$	221°C
56	CONHEt	Me	OMe	NH_2	72	HCl, $0.45H_2O$	221°C
57	$CONHCH_2CO_2$	Me	OMe	NH_2	91	HCl, $1.05H_2O$	196°C

Example 58

(4-Amino-3-methoxyphenyl){1-[(2-chlorobenzyl)oxy]-2-methylindolizin-3-yl}methanone hydrochloride

47 mg of 10% Pd/C are added to 470 mg (1.04 mmol) of {1-[(2-chlorobenzyl)oxy]-2-methylindolizin-3-yl}(3-methoxy-4-nitrophenyl)methanone in 5 ml of methanol and 10 ml of dichloromethane, followed by 253 µl (5.21 mmol) of hydrazine hydrate, and the medium is stirred at room temperature overnight. The reaction medium is filtered on talc and the catalyst is washed with methanol. The filtrate is concentrated under reduced pressure. The residue is taken up in ethyl acetate, the organic phase is washed with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure. 460 mg of a yellow powder are recovered. The product is salified by dissolving the powder obtained above in a mixture of ethyl acetate and methanol, and then 1.25ml (1.2 equivalents) of 1 N hydrochloric acid in ethyl ether are added. After addition of ethyl ether, the precipitate obtained is filtered, washed with ethyl ether and then dried.
440 mg of a yellow powder are recovered in the form of the hydrochloride $0.65H_2O$.

Yield: 90%

Melting point: 177°C

Examples 59 to 76

By carrying out the procedure according to the preparation described in Example 58, the compounds described in Table IV below are synthesized by reducing the nitro functional group of the compounds of formula Ia with hydrazine hydrate in the presence of 10% Pd/C as catalyst.

TABLE IV

Example	A	R_1	R_2	R_3	R_4	Yield (%)	Salts	Malting point or mass spectro. (MH+)
59	CO	OBn	C_6H_5	OMe	NH_2	94	HCl, $0.2H_2O$	207°C
60	CO	$O(CH_2)_2NMe_2$	Me	OMe	NH_2	31	2HCl, $2H_2O$	246°C
61	CO	OBn-4-Cl	Me	OMe	NH_2	99	HCl	177°C
62	CO	OBn-3-OMe	Me	OMe	NH_2	95	HCl	181°C
63	CO	OBn-4-OMe	Me	OMe	NH_2	99	HCl, $0.3H_2O$	128°C
64	CO	OBn-2-OMe	Me	OMe	NH_2	99	HCl	164°C
65	CO	OBn-3-CO_2Me	Me	OMe	NH_2	75	HCl	185°C
66	CO	OBn-4-CO_2Me	Me	OMe	NH_2	93	HCl, $1H_2O$	160°C
67	CO	OBn-3-Cl	Me	OMe	NH_2	96	HCl	175°C
68	CO	N(Me)Bn	Me	OMe	NH_2	78	HCl, $1.6H_2O$	114°C
69	CO	NHBOC	Me	OMe	NH_2	95	base	MH^+= 396.4
70	CO	NHMe	Me	OMe	NH_2	88	HCl, $1.15H_2O$	210°C
71	CO	$NHSO_2Me$	Me	OMe	NH_2	83	HCl	228°C

Example	A	R_1	R_2	R_3	R_4	Yield (%)	Salts	Melting point or mass spectro. (MH+)
72	CO	OMe	Me	NH_2	CO_2Me	72	-	135°C
73	SO_2	OMe	Me	H	NH_2	66	-	157°C
74	CO	OCH_2cPr	Me	OMe	NH_2	99	HCl	181°C
75	CO	OiBu	Me	OMe	NH_2	60	HCl	103°C
76	CO	NMe_2	Me	OMe	NH_2	80	2HCl, $0.2H_2O$	171°C

Example 77

[1-(2-Hydroxyethoxy)-2-methylindolizin-3-yl](3-methoxy-4-nitrophenyl)methanone

1.52 ml of 1 N sodium hydroxide are added to 420 mg (1.02 mmol) of 2-{[3-(3-methoxy-4-nitrobenzoyl)-2-methylindolizin-1-yl]oxy}ethyl acetate, a compound of Example 35, dissolved in 6 ml of dioxane, and the medium is stirred at room temperature for 6 hours. The reaction medium is poured over water and ethyl acetate. The organic phase is separated after settling out, washed with water, dried over sodium sulphate and concentrated under reduced pressure. 340 mg of an orange-coloured powder are obtained, which powder is used without further purification in the subsequent nitro reduction step.

Yield: 90%

Melting point: 142°C

Example 78

Sodium salt of 4-[(1-methoxy-2-methyl-3-indolizinyl)carbonyl]benzoic acid

2.45 ml of 1 N sodium hydroxide are added to 720 mg (2.23 mmol) of methyl 4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]benzoate, a compound of Example 8, in solution in 15 ml of methanol plus 15 ml of dioxane, and the medium is stirred at room temperature overnight. The reaction medium is

concentrated under reduced pressure. The residue is taken up in water, washed with ethyl ether and separated after settling out. The aqueous phase is acidified with 1 N hydrochloric acid and extracted with dichloromethane.

The organic phase is washed with water, dried over sodium sulphate and concentrated under reduced pressure. 700 mg of an orange-coloured powder are obtained, which powder is suspended in 20 ml of methanol and then one equivalent of 1 N sodium hydroxide is added. The solution obtained is concentrated under reduced pressure. The residue is crystallized from acetone. The product is filtered off, washed with acetone and then with ethyl ether, dried, and 680 mg of a yellow powder are obtained.

Yield (Na salt): 92%

Melting point > 400°C

Examples 79 to 84

By carrying out the procedure according to the method described in Example 78, the compounds described in Table V below are synthesized by saponification of the ester functional group of the compounds of formula Id.

TABLE V

Example	R_1	R_2	R_3	R_4	Yield (%)	Salts	Melting point
79	OMe	Me	CO_2H	H	76	Na	218°C
80	OMe	Me	NO_2	CO_2H	85	Na	265°C
81	OMe	Me	NH_2	CO_2H	77	Na	315°C
82	OBn-3-OMe	Me	H	CO_2H	81	Na, $0.7H_2O$	268°C
83	OMe	Me	OMe	CO_2H	87	Na, $1H_2O$	.235°C
84	OMe	Me	H	CH_2CO_2H	91	Na, $0.7H_2O$	248°C

Example 85

3-(4-Amino-3-methoxybenzoyl)-2-methylindolizin-1-ylcarboxylic acid

30 ml of 2 N sodium hydroxide are added to 2.1 g (5.96 mmol) of ethyl 3-(4-amino-3-methoxybenzoyl)-2-methyl-1-indolizinecarboxylate in solution in 30 ml of dioxane, and the medium is heated under reflux for 20 hours. The reaction medium is concentrated under reduced pressure.

The residue is taken up in water, washed with ethyl ether and separated after settling out. The aqueous phase is acidified to pH 6.5 with a 10% aqueous potassium hydrogen sulphate solution and extracted with ethyl acetate. The organic phase is washed with water, dried over sodium sulphate and concentrated under reduced pressure. 1.8 g of a yellow powder are obtained.

Yield: 93%

Two salts of the compound are then prepared:
Sodium salt, monohydrate, melting point: 224°C;
hydrochloride, melting point: 213°C

Examples 86 to 90

By carrying out the procedure according to the preparation described above, the compounds described in Table VI below are synthesized by saponification of the ester functional group contained in the substituent R_1 of the compounds of formula Id, in which A represents a radical -CO-, with sodium hydroxide.

TABLE VI

Example	R_1	R_2	R_3	R_4	Yield (%)	Salts	Melting point (°C)
86	OCH_2CO_2H	Me	3-OMe	4-NH_2	91	-	227°C
87	$CONHCH_2CO_2H$	Me	3-OMe	4-NH_2	90	Na, 0.95H_2O	297°C
88	OBn-3-CO_2H	Me	3-OMe	4-NH_2	84	Na,1.25H_2O	207°C
89	OBn-4-CO_2H	Me	3-OMe	4-NH_2	76	Na, 0.7H_2O	216°C
90	CO_2H	C_6H_5	3-OMe	4-NH_2	84	Na, 1.25H_2O	305°C

Example 91

Disodium salt of 3-(4-carboxybenzoyl)-2-methyl-indolizin-1-ylcarboxylic acid

7.47 ml of 1 N sodium hydroxide are added to 910 mg (2.49 mmol) of ethyl 3-[4-(methoxycarbonyl)benzoyl]-2-methylindolizin-1-ylcarboxylate in solution in 20 ml of dioxane plus 20 ml of ethanol, and the medium is heated under reflux

for 6 hours. The reaction medium is concentrated under reduced pressure. The residue is taken up in water, washed with ethyl ether and separated after settling out. The aqueous phase is acidified with 1 N hydrochloric acid and extracted with ethyl acetate. The organic phase is washed with water, dried over sodium sulphate and concentrated under reduced pressure.
650 mg of a yellow powder are obtained, which powder is suspended in 20 ml of methanol, and then 4.02 ml of 1 N sodium hydroxide (2 eq.) are added. The solution obtained is concentrated under reduced pressure. The residue is crystallized from acetone. The product is filtered off, washed with acetone and then with ethyl ether and dried. 700 mg of a yellow powder are obtained.

Yield, disodium salt, dihydrate: 81%

Melting point: > 400°C

Examples 92 and 93

By carrying out the procedure according to Example 91, the compounds described in Table VII below are synthesized by saponification of the ester functional groups contained in the substituents R_1 and R_4 of the compounds of formula I, in which A represents a radical -CO-, with 1 N sodium hydroxide.

TABLE VII

Example	R_1	R_2	R_3	R_4	Yield (%)	Salts	Melting point (°C)
92	OCH_2CO_2H	Me	H	CO_2H	90	2Na, $2H_2O$	>400°C
93	CO_2H	Me	OMe	CO_2H	96	2Na.1.5H_2O	323°C

Example 94

(4-{[3-(Dibutylamino)propyl]amino}-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone hydrochloride

700 mg (2.25 mmol) of (4-amino-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone, a compound described in Example 48, dissolved in 5 ml of tetrahydrofuran, are added to 278.4 mg (2.25 mmol) of potassium *tert*-butoxide in 5 ml of tetrahydrofuran, and the medium is stirred for 15 minutes at room temperature.

510.5 mg (2.48 mmol) of dibutylaminopropyl chloride in 5 ml of tetrahydrofuran are then added, and the medium is heated under reflux overnight.

The reaction medium is cooled and poured over water and then extracted with ethyl acetate. The organic phase is separated after settling out, washed with water, dried over sodium sulphate and concentrated under reduced pressure.

The product is purified by chromatography on a silica column, eluting with a dichloromethane/acetone (9/1) and then (1/1) mixture.

700 mg of an orange-coloured resin are obtained, which resin is salified in ethyl ether by adding one equivalent of 1 N hydrochloric acid in ethyl ether.

The crystals obtained are filtered off, washed with ethyl ether and dried. An orange-coloured powder is obtained in the form of the hydrochloride, 1.25H_2O.

Yield: 65%

Melting point: 51°C

Example 95

[3-Methoxy-4-(methylamino)phenyl](1-methoxy-2-methylindolizin-3-yl)methanone hydrochloride

This compound is obtained according to the same procedure as that described in Example 94, by alkylating (4-amino-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone with methyl iodide. A yellow powder is obtained.

Yield: 45%

Melting point: 172°C

Example 96

(4-{[3-(Dibutylamino)propyl]amino}-3-methoxyphenyl)(1-methoxy-2-phenylindolizin-3-yl)methanone dihydrochloride

Obtained according to the same procedure as that described in Example 94, by alkylating (4-amino-3-methoxyphenyl)(1-methoxy-2-phenylindolizin-3-yl)methanone, a compound of Example 49, with dibutylaminopropyl chloride. An orange-coloured powder is obtained (dihydrochloride: $1.3H_2O$).

Yield: 37%

Melting point: 158°C

Example 97

Ethyl 2-{2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]anilino}acetate

This compound was obtained according to the same procedure as that described in Example 94, by alkylating (4-amino-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone, a compound of Example 48, with ethyl bromoacetate. A yellow powder is obtained.

Yield: 60.5%

Melting point: 125°C

Example 98

2-{2-Methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]anilino}acetic acid

3.15 ml of 1 N sodium hydroxide are added to 1 g (2.52 mmol) of ethyl 2-{2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]anilino}acetate, a compound obtained in Example 97, in solution in 10 ml of ethanol, and the medium is stirred at room temperature overnight. The reaction medium is concentrated under reduced pressure. The residue is taken up in water, washed with ethyl ether and separated after settling out. The aqueous phase is neutralized with 1 N hydrochloric acid. The precipitate formed is filtered off, washed with water, dried and then taken up in ethyl ether, filtered and dried. A yellow powder is obtained.

Yield: 48.5%

Melting point: 196°C

Example 99

Ethyl 2-{2-methoxy-4-[(1-methoxy-2-phenylindolizin-3-yl)carbonyl]anilino}acetate

This compound was obtained according to the method described in Example 94, by alkylating (4-amino-3-methoxyphenyl)(1-methoxy-2-phenylindolizin-3-yl)methanone, a compound of Example 49, with ethyl bromoacetate. A yellow powder is obtained.

Yield: 78%

Melting point: 132°C

Example 100

2-{2-Methoxy-4-[(1-methoxy-2-phenylindolizin-3-yl)carbonyl]anilino}acetic acid

Obtained according to the same procedure as the compound of Example 98, by saponification of ethyl 2-{2-methoxy-4-[(1-methoxy-2-phenylindolizin-3-yl)carbonyl]anilino}acetate, a compound of Example 99, with 1 N sodium hydroxide. A yellow powder is obtained.

Yield: 80%

Melting point: 206°C

Example 101

3-(Dibutylamino)-*N*-{2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]phenyl}propanamide hydrochloride

2.5 ml (17.7 mmol) of triethylamine are added to 2.5 g (8.06 mmol) of (4-amino-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone, a compound of Example 48, in 20 ml of dichloromethane cooled to 5°C, followed by 846 µl (8.86 mmol) of 3-chloropropionyl chloride in solution in 10 ml of dichloromethane, and the medium is stirred for 3 hours at room temperature. The reaction medium is washed with water and then with a saturated aqueous sodium chloride solution, dried

over sodium sulphate and concentrated under reduced pressure.

The residue obtained is dissolved in 40 ml of ethanol and 1.7 g (13.2 mmol) of dibutylamine are added, and then the medium is heated under reflux for 7 hours. The reaction medium is concentrated under reduced pressure. The product is purified by chromatography on a silica column, eluting with a dichloromethane/methanol (98:2) mixture. 2.6 g of product are obtained, which product is salified by adding 1 N hydrochloric acid in ethyl ether. A yellow powder is obtained (hydrochloride, $0.25H_2O$).

Yield: 65%

Melting point: 82°C

Example 102

3-(Dibutylamino)-*N*-{2-methoxy-4-[(1-methoxy-2-phenylindolizin-3-yl)carbonyl]phenyl}propanamide hydrochloride

This compound was obtained according to the same procedure as that described in Example 101, by acylation of (4-amino-3-methoxyphenyl)(1-methoxy-2-phenylindolizin-3-yl)methanone with 3-chloropropionyl chloride, followed by amination with dibutylamine. A yellow powder is obtained (hydrochloride, hemihydrate),

Yield: 52%

Melting point: 190°C

Example 103

***N*-{2-Methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]phenyl}acetamide**

This compound was obtained according to the same procedure as that described in Example 101, by acylation of (4-amino-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone, a compound of Example 48, with acetyl chloride. The product is purified by flash chromatography on silica, eluting with a dichloromethane/methanol (99:1) mixture. A yellow powder is obtained ($0.3H_2O$).

Yield: 73%

Melting point: 180°C

Example 104

Ethyl 2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]phenylcarbamate

This compound was obtained according to the same procedure as that described in Example 101 by acylation of (4-amino-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone with ethyl chloroformate. The product is purified by flash chromatography on silica, eluting with dichloromethane. A yellow powder is obtained.

Yield: 41%

Melting point: 140°C

Example 105

Ethyl 2-{[3-(dibutylamino)propanoyl]-2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]anilino}acetate hydrochloride

1 g (2.03 mmol) of 3-(dibutylamino-*N*-{2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]phenyl}propanamide, a compound of Example 101, in solution in 10 ml of dimethylformamide, is added dropwise to 89.1 mg (2.23 mmol) of sodium hydride, at 60% as a dispersion in oil, in 10 ml of dimethylformamide, and then the medium is stirred at room temperature for 1 hour. 247 µl (2.23 mmol) of ethyl bromoacetate are then added, and the medium is stirred at room temperature overnight.

The reaction medium is poured over water and ethyl acetate. The organic phase is separated after settling out, washed with water, dried over sodium sulphate and concentrated under reduced pressure. The product is purified by flash chromatography on a silica column, eluting with a dichloromethane/methanol (97/3) mixture. 850 mg of an oil are obtained, which oil is dissolved in ethyl ether and salified by adding one equivalent of 1 N hydrochloric acid in ethyl ether. Yellow crystals are obtained (hydrochloride, hydrate).

Yield: 72%

Melting point: 67°C

<u>Example 106</u>

Hydrochloride of 2-{[3-(dibutylamino)propanoyl]-2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]anilino}acetic acid

586 µl of 1 N sodium hydroxide are added to 340 mg (0.586 mmol) of ethyl 2-{[3-(dibutylamino)propanoyl]-2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]anilino}acetate obtained in Example 105, in solution in 5 ml of ethanol, and the medium is stirred at room temperature overnight. The reaction medium is concentrated under reduced pressure. The residue is taken up in water, washed with ethyl ether and separated after settling out. The aqueous phase is neutralized with 1 N hydrochloric acid, and extracted with dichloromethane. The organic phase is dried over sodium sulphate and concentrated under reduced pressure.

The product is purified by flash chromatography on a silica column, eluting with a dichloromethane/methanol (8:2) mixture. 230 mg of an oil are obtained, which oil is dissolved in ethyl acetate and salified by adding one equivalent of 1 N hydrochloric acid in ethyl ether. A yellow powder is obtained (hydrochloride, $0.6H_2O$)

Yield: 71%

Melting point: 151°C

Example 107

Ethyl 2-{[3-(dibutylamino)propanoyl]-2-methoxy-4-[(1-methoxy-2-phenyl-3-indolizinyl)carbonyl]anilino}acetate hydrochloride

Obtained according to the method described in previous Example 105, by alkylating 3-(dibutylamino)-*N*-{2-methoxy-4-[(1-methoxy-2-phenylindolizin-3-yl)carbonyl]phenyl}propanamide, a compound of Example 102, with ethyl bromoacetate. A yellow powder (hydrochloride) is obtained after salification with 1 N hydrochloric acid in ethyl ether.

Yield: 55%

Melting point: 64°C

Example 108

Hydrochloride of 2-{[3-(dibutylamino)propanoyl]-2-methoxy-4-[(1-methoxy-2-phenylindolizin-3-yl)carbonyl]anilino}acetic acid

Obtained acccording to the same procedure as that of Example 106, by saponification of ethyl 2-{[3-(dibutylamino)propanoyl]-2-methoxy-4-[(1-methoxy-2-phenylindolizin-3-yl)carbonyl]anilino}acetate, a compound of Example 107, with 1 N sodium hydroxide. A yellow powder is obtained after salification with 1 N hydrochloric acid in ethyl ether.

Yield: 75%

Melting point: 113°C

Example 109

2-(Dibutylamino)-*N*-{2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]phenyl}-1-ethanesulphonamide hydrochloride

471.5 µl (3.38 mmol) of triethylamine are added to 1 g (3.22 mmol) of (4-amino-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone in 15 ml of dichloromethane, followed by 346.9 µl (3.22 mmol) of 2-chloroethylsulphonyl chloride in solution in 5 ml of dichloromethane, and the medium is stirred at room temperature overnight. The reaction medium is washed with water and then with a saturated aqueous sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure.

The residue obtained is dissolved in 10 ml of ethanol. 375 mg (2.9 mmol) of dibutylamine are added and the medium is heated under reflux for 4 hours. The reaction medium is concentrated under reduced pressure. The product is purified by chromatography on a silica column, eluting with a dichloromethane/methanol (98:2) mixture. 1.18 g of product are obtained, which product is salified by adding 1 N hydrochloric acid in ethyl ether. A yellow powder is obtained (hydrochloride, hemihydrate).

Yield: 69%

Melting point: 91°C

Example 110

2-(Dibutylamino)-*N*-{2-methoxy-4-[(1-methoxy-2-phenylindolizin-3-yl)carbonyl]phenyl}-1-ethanesulphonamide hydrochloride

This compound is obtained according to the same procedure as the compound of Example 109, by sulphonylation of (4-amino-3-methoxyphenyl)(1-methoxy-2-phenylindolizin-3-yl)methanone with 2-chloroethylsulphonyl chloride, followed by amination with dibutylamine. A yellow powder is obtained (hydrochloride, hemihydrate).

Yield: 63%

Melting point: 111°C

Example 111

***N*-{2-Methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]phenyl}methanesulphonamide**

Obtained according to the same procedure as the compound of Example 109, by sulphonylation of (4-amino-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone with methanesulphonyl chloride. The product is purified by chromatography on a silica column, eluting with a toluene/ethyl acetate (7:3) mixture. A yellow powder is obtained.

Yield: 67%

Melting point: 165°C

Example 112

Ethyl 3-{3-methoxy-4-[(methylsulphonyl)amino]benzoyl}-2-methylindolizin-1-ylcarboxylate

This compound was obtained according to the same procedure as that described in Example 109, by sulphonylation of ethyl 3-(4-amino-3-methoxybenzoyl)-2-methylindolizin-1-ylcarboxylate, a compound of Example 51, with methanesulphonyl chloride. The product is purified by chromatography on a silica column, eluting with a toluene/ethyl acetate (8:2) mixture. A yellow powder is obtained.

Yield: 57%

Melting point: 178°C

Example 113

Sodium salt of 3-{3-methoxy-4-[(methylsulphonyl)amino]benzoyl}-2-methylindolizin-1-ylcarboxylic acid

1 ml of caustic soda is added to 290 mg (0.675 mmol) of ethyl 3-{3-methoxy-4-[(methylsulphonyl)amino]benzoyl}-2-methylindoliz-1-ylcarboxylate in 7 ml of dioxane plus 7 ml of water, and the medium is heated under reflux for 6 hours.

The medium is cooled, poured over water and neutralized with an aqueous potassium hydrogen sulphate

solution, and then extracted with ethyl acetate. The organic phase is washed with water, dried over sodium sulphate and concentrated under reduced pressure.

220 mg of a yellow powder are obtained. The product is salified by adding one equivalent of 1 N sodium hydroxide to a suspension of the product in water and stirring at room temperature until dissolution is obtained.

The solution obtained is then freeze-dried. A yellow freeze-dried product is recovered (Na salt, 1.85H_2O).

Yield: 81%

Mass spectrometry (ES+ mode) MH^+ = 403.2

Example 114

Hydrochloride of 2-{{[2-(dibutylamino)ethyl]sulphonyl}-2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]anilino}acetic acid

Step A

Benzyl 2-{{[2-(dibutylamino)ethyl]sulphonyl}-2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]anilino}acetate

125 mg (0.906 mmol) of potassium carbonate are added to 400 mg (0.755 mmol) of 2-(dibutylamino)-*N*-{2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]phenyl}-1-ethanesulphonamide, a compound of Example 109, in solution in 10 ml of dimethylformamide,

followed by 142 µl (0.906 mmol) of benzyl bromoacetate, and the medium is heated at 60°C for 1 hour. The reaction medium is poured over water and ethyl acetate. The organic phase is separated after settling out, washed with water, dried over sodium sulphate and concentrated under reduced pressure. The product is purified by flash chromatography on a silica column, eluting with a dichloromethane/methanol (98:2) mixture. 440 mg of an oil are obtained, which oil is used directly in the next step.

Yield: 86%

Step B

1.3 ml (12.7 mmol) of cyclohexene are added to 430 mg (0.634 mmol) of benzyl 2-{{[2-(dibutylamino)ethyl]sulphonyl}-2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]anilino}acetate in 5 ml of ethanol, in the presence of 100 mg of 10% Pd/C, and the medium is heated under reflux for 3 hours. The reaction medium is cooled. The catalyst is filtered off and the filtrate is concentrated under reduced pressure. The product is purified by flash chromatography on a silica column, eluting with a dichloromethane/methanol (9:1) mixture. 250 mg of an oil are obtained, which oil is dissolved in ethyl acetate and salified by adding one equivalent of 1 N

hydrochloric acid in ethyl ether. An orange-coloured powder is obtained (hydrochloride, dihydrate).

Yield: 67%

Melting point: 85°C

<u>Example 115</u>

Benzyl 2-{{[2-(dibutylamino)ethyl]sulphonyl}-2-methoxy-4-[(1-methoxy-2-phenylindolizin-3-yl)carbonyl]anilino}acetate hydrochloride

This compound was obtained according to the same procedure as Example 114, Step A, by alkylating 2-(dibutylamino)-*N*-{2-methoxy-4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]phenyl}-1-ethanesulphonamide, with benzyl bromoacetate.

A yellow powder (hydrochloride, hemihydrate) is obtained after salification with 1 N hydrochloric acid in ethyl ether.

Yield: 55%

Melting point: 95°C

<u>Example 116</u>

Hydrochloride of 2-{{[2-(dibutylamino)ethyl]sulphonyl}-2-methoxy-4-[(1-methoxy-2-phenylindolizin-3-yl)carbonyl]anilino}acetic acid

This compound was obtained according to the same procedure as Example 114, Step B, by hydrogenating benzyl 2-{{[2-(dibutylamino)ethyl]sulphonyl}-2-methoxy-

4-[(1-methoxy-2-phenylindolizin-3-yl)carbonyl]anilino}acetate, a compound of Example 115, with cyclohexene in the presence of Pd/C in ethanol. A yellow powder (hydrochloride, $1.5H_2O$) is obtained after salification with 1 N hydrochloric acid in ethyl ether.

Yield: 75%

Melting point: 113°C

Example 117

Study of the binding of ^{125}I-b-FGF to the purified receptor FGF R α IIIc by the proximity scintillation method

NBS plates (NBS plate 96 well solid white CORNING 3600) are coated with 100 µl of 0.1% gelatine per well, for 2 hours at 37°C. At the end of the incubation, the coating is removed, the plates are rinsed and thoroughly dried. 100 µl of binding buffer (40 mM Bis Tris buffer, pH 7.0) are distributed into the plates.

Dilutions of the compounds of the invention are distributed into the wells in an amount of 10 µl/well. There are then distributed 10 µl/well of b-FGF (AMERSHAM ARM 35050) and 10 µl/well of FGF R α IIIc (R&D Systems 658 FR). Next, there are added 10 µl/well of ^{125}I-b-FGF (Dupont NEN NEX 268 - specific activity > 70 µCi) and 50 µl/well of SPA beads

(AMERSHAM RPQN 00019). The plate is shaken for a few seconds and it is incubated for 60 minutes at 37°C, protected from light.

At the end of the incubation, the plate is read in a MIBROBETA TRILUX radioactivity counter (WALLAC - PERKINELMER).

The compounds of the invention demonstrated a specific activity of between 10^{-6} M and 10^{-9} M.

Example 118

Effects of the compounds of formula I on the proliferation of HUVECs versus 30 ng/ml of b-FGF

Coat the 24-well plates (FALCON PRIMARIA) with 200 µl of a solution of fibronectin (50 µg/ml prepared in PBS)/well.

Inoculate in an amount of 30 000 cells/ml/well in an RPMI 1640 medium + 10% FCS + 1% glutamine + heparin-ECGF (HE) mixture.

Incubate at 37°C, 5% CO_2, the time required for the cells to adhere.

Dilute 62.5 µl of a solution containing 50 µg/ml of b-FGF (Amersham, ARM 33 050) to 1/16 with a mixture composed of PBS and BSA so as to obtain a solution having a concentration of 3125 ng/ml. Distribute 10 µl of this solution in the wells (i.e. 31.25 ng/well/ml of b-FGF).

Dissolve the products and prepared solutions in DMSO/reaction medium having a final concentration of 1 μM final at 10^{-7} M.

After adhesion of the cells for 6 hours at 37°C in the presence of 5% CO_2, the medium is replaced with RPMI 1640 0.1% FSC + glutamine + HE.

For the derivatization, there is used as negative control 0.1% FCS, as positive control 0% FCS and as control 0.1% FCS + 10 ng/ml of b-FGF. Incubation is then carried out for 24 hours at 37°C in the presence of 5% CO_2.

The second day, the cells are rinsed with 1 ml PBS and 200 μl of trypsin, and they are then recovered in isotone. Counting is carried out (n > 9 μm).

In this test of proliferation of endothelial cells induced by b-FGF, the compounds of the invention demonstrated a specific activity of between 10^{-5} M and 10^{-9} M.

Example 119

Model of angiogenesis *in vitro*

Prepare the gels by distributing into each chamberslide well (Biocoat Cellware rat tail collagen, Type I, 8-well culturesides: Becton Dickinson 354630) 160 μl of matrigel diluted 1/6 (Growth factor reduced Matrigel: Becton Dickinson 356230) in collagen (Rat

Tail Collagen, type I: Becton Dickinson 354236). Allow to gel for 1 hour at 37°C.

Inoculate the human vein endothelial cells (HUVEC ref: C-015-10C - cascade Biologics, INC) or porcine aortic endothelial cells (PAEC) at $15 \cdot 10^3$ cells/well in 400 µl of EBM medium (Clonetics C3121) + 2% FBS + hEGF 10 µg/ml for the HUVECs and DMEM + 3% FCS + 2 mM glutamine + 1 mM sodium pyruvate + 1% nonessential amino acids (GIBCO) for the PAECs.

Stimulate with b-FGF (TEBU/Peprotech) 10 ng/ml in the presence or otherwise of the products of the invention for 24 h at 37°C in the presence of 5% CO_2.

After 24 hours, fix the cells and stain the slide with the Masson trichrome before examination under the microscope X4 lens and image analysis (BIOCOM - Visiolab 2000 software).

For the test of angiogenesis *in vitro* induced by b-FGF, the compounds of the invention demonstrated a specific activity of between 10^{-7} M and 10^{-11} M.

Example 120

Model of inflammatory angiogenesis in mice

Angiogenesis is required for the development of chronic inflammatory diseases such as rheumatoid arthritis, IBD, but also for the development of solid tumours. The formation of new vessels not only allows

the perfusion of pathological tissues, but also the transport of cytokines responsible for establishing the chronicity of the disease.

The model described by Colville-Nash P. et al., (*D. JPET.*, 1995, Vol. 274 No. 3, pp. 1463-1472) makes it possible to study pharmacological agents capable of modulating the appearance of angiogenesis.

The animals, nonconsanguineous white mice of about 25 g, are anaesthetized with sodium pentobarbital (60 mg/kg; Sanofi Nutrition Santé Animale) by the intraperitoneal route.

An air pouch is created on the back of the mice by injecting 3 ml of air subcutaneously.

After becoming conscious, the animals receive a treatment, in general by force-feeding, and receive an injection of 0.5 ml of Freund's adjuvant (Sigma) with 0.1% croton oil (Sigma) in the pouch.

Seven days later, the mice are again anaesthetized and placed on a heating plate at 40°C. One ml of carmine red (5% in 10% gelatine - Aldrich Chemicals) is injected into the tail vein. The animals are then placed at 4°C for 2-3 hours.

The skins are then removed and dried for 48 hours in an oven at 56°C. The dry tissues are weighed and placed in 1.8 ml of digestion buffer (2 mM dithiothreitol, 2 mM Na_2HPO_4, 1 mM EDTA, 12 U/ml papain) for 24 hours.

The stain is then dissolved in 0.2 ml of 5 M NaOH. The skins are centrifuged at 2000 g for 10 min. The supernatants are filtered on 0.2 µm cellulose acetate membranes. The filtrates are read in a spectrophotometer at 492 nm against a carmine red calibration series.

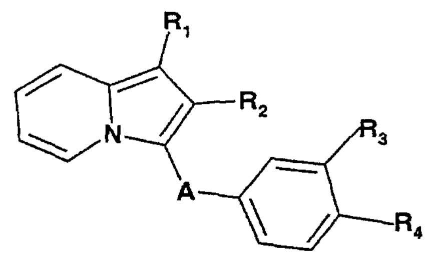
Two parameters are studied: the dry weight of the granuloma and the quantity of stain after digestion of this tissue.

The results are expressed as mean values (± SEM). The differences between the groups are tested with an ANOVA followed by Dunnet's test for which the reference group is the "solvent control" group.

The compounds of the invention are active by the oral route at doses of 0.1 to 100 mg/kg.

CLAIMS

1. Compounds of formula I,



(I)

in which

- **R_1** represents a hydroxyl radical, a linear or branched alkoxy radical of 1 to 5 carbon atoms, a carboxyl radical, an alkoxycarbonyl radical of 2 to 6 carbon atoms or a radical of formula:
  - $-NR_5R_6$
  - $-NH-SO_2-Alk$
  - -NH-CO-Phe
  - -NH-CO-Alk
  - $-NH-CO_2-Alk$
  - $-O-(CH_2)_n-cAlk$
  - $-O-Alk-COOR_7$
  - $-O-Alk-O-R_8$
  - -O-Alk-OH
  - $-O-Alk-C(NH_2):NOH$
  - $-O-Alk-NR_5R_6$
  - -O-Alk-CN

- $-O-(CH_2)_n-Ph$
- $-O-Alk-CO-NR_5R_6$
- $-CO-NH-(CH_2)_m-COOR_7$
- -CO-NH-Alk
- -CO-NH-Ph

in which

- Alk represents an alkyl radical or a linear or branched alkylene radical of 1 to 5 carbon atoms,
- cAlk represents a cycloalkyl radical of 3 to 6 carbon atoms,
- n represents an integer from 0 to 5,
- m represents an integer from 1 to 5,
- R_5 and R_6, which are identical or different, each represent a hydrogen atom, a linear or branched alkyl radical of 1 to 5 carbon atoms or a benzyl radical,
- R_7 represents a hydrogen atom or an alkyl radical of 1 to 5 carbon atoms,
- R_8 represents an alkyl radical of 1 to 5 carbon atoms or a radical -CO-Alk,
- Ph represents a phenyl radical which is optionally substituted with one or more halogen atoms, with one or more alkoxy radicals of 1 to 5 carbon atoms, with one or more carboxyl

radicals or with one or more alkoxycarbonyl radicals of 2 to 6 carbon atoms,

- **R_2** represents an alkyl radical of 1 to 5 carbon atoms, a cycloalkyl radical of 3 to 6 carbon atoms or a phenyl radical which is optionally substituted with one or more halogen atoms, with one or more alkoxy radicals of 1 to 5 carbon atoms, with one or more carboxyl radicals or with one or more alkoxycarbonyl radicals of 2 to 6 carbon atoms,
- **A** represents a radical -CO-, -SO- or $-SO_2-$,
- **R_3** and **R_4**, which are identical or different, each represent a hydrogen atom, an alkoxy radical of 1 to 5 carbon atoms, an amino radical, a carboxyl radical, an alkoxycarbonyl radical of 2 to 6 carbon atoms, a hydroxyl radical, a nitro radical, a hydroxyamino radical, a radical of formula
  - $-Alk-COOR_7$
  - $-NR_5R_6$
  - $-NH-Alk-COOR_7$
  - -NH-COO-Alk
  - $-N(R_{11})-SO_2-Alk-NR_9R_{10}$
  - $-N(R_{11})-SO_2-Alk$
  - $-N(R_{11})-Alk-NR_5R_6$
  - $-N(R_{11})-CO-Alk-NR_9R_{10}$
  - $-N(R_{11})-CO-Alk$
  - -NH-Alk-HetN

- -O-Alk-NR_9R_{10}
- -O-Alk-CO-NR_5R_6
- -O-Alk-HetN

in which n, m, Alk, R_5, R_6 and R_7 have the meaning given above for R_1, and

- R_9 and R_{10}, which are identical or different, each represent a hydrogen atom or an alkyl radical of 1 to 5 carbon atoms,
- R_{11} represents a hydrogen atom or a radical -Alk-$COOR_{12}$ where R_{12} represents a hydrogen atom, an alkyl radical of 1 to 5 carbon atoms or a benzyl radical,
- HetN represents a 5- or 6-membered heterocycle containing at least one nitrogen atom and optionally another heteroatom chosen from nitrogen and oxygen,

or R_3 and R_4 form together a 5- to 6-membered unsaturated heterocycle, provided, however, that when R_3 represents an alkoxy radical and R_4 represents a radical -O-Alk-NR_9R_{10} or a hydroxyl radical, R_1 does not represent an alkoxy radical, optionally in the form of one of their pharmaceutically acceptable salts.

2. Compounds of formula I, according to Claim 1, in which

- **R_1** represents a hydroxyl radical, a linear or branched alkoxy radical of 1 to 5 carbon atoms, a

carboxyl radical, an alkoxycarbonyl radical of 2 to 6 carbon atoms or a radical of formula:

- $-NR_5R_6$
- $-NH-SO_2-Alk$
- -NH-CO-Ph
- -NH-CO-Alk
- $-NH-CO_2-Alk$
- $-O-(CH_2)_n-cAlk$
- $-O-Alk-COOR_7$
- $-O-Alk-O-R_8$
- -O-Alk-OH
- $-O-Alk-NR_5R_6$
- -O-Alk-CN
- $-O-(CH_2)_n-Ph$
- $-O-Alk-CO-NR_5R_6$
- $-CO-NH-(CH_2)_m-COOR_7$
- -CO-NH-Alk
- -CO-NH-Ph

in which

- Alk represents an alkyl radical or a linear or branched alkylene radical of 1 to 5 carbon atoms,
- cAlk represents a cycloalkyl radical of 3 to 6 carbon atoms,
- n represents an integer from 0 to 5,
- m represents an integer from 1 to 5,

- R_5 and R_6, which are identical or different, each represent a hydrogen atom, a linear or branched alkyl radical of 1 to 5 carbon atoms or a benzyl radical,
- R_7 represents a hydrogen atom or an alkyl radical of 1 to 5 carbon atoms,
- R_8 represents an alkyl radical of 1 to 5 carbon atoms or a radical -CO-Alk,
- Ph represents a phenyl radical which is optionally substituted with one or more halogen atoms, with one or more alkoxy radicals of 1 to 5 carbon atoms, with one or more carboxyl radicals or with one or more alkoxycarbonyl radicals of 2 to 6 carbon atoms,

- **R_2** represents an alkyl radical of 1 to 5 carbon atoms, a cycloalkyl radical of 3 to 6 carbon atoms or a phenyl radical which is optionally substituted with one or more halogen atoms, with one or more alkoxy radicals of 1 to 5 carbon atoms, with one or more carboxyl radicals or with one or more alkoxycarbonyl radicals of 2 to 6 carbon atoms,
- **A** represents a radical -CO- or $-SO_2-$,
- **R_3** and **R_4**, which are identical or different each represent a hydrogen atom, an alkoxy radical of 1 to 5 carbon atoms, an amino radical, a carboxyl radical, an alkoxycarbonyl radical of 2 to 6

carbon atoms, a nitro radical, a hydroxyamino radical, a radical of formula

- $-Alk-COOR_7$
- $-NR_5R_6$
- $-NH-Alk-COOR_7$
- $-NH-COO-Alk$
- $-N(R_{11})-SO_2-Alk-NR_9R_{10}$
- $-N(R_{11})-SO_2-Alk$
- $-N(R_{11})-Alk-NR_5R_6$
- $-N(R_{11})-CO-Alk-NR_9R_{10}$
- $-N(R_{11})-CO-Alk$
- $-NH-Alk-HetN$

in which n, m, Alk, R_5, R_6 and R_7 have the meaning given above for R_1, and

- R_9 and R_{10}, which are identical or different, each represent a hydrogen atom or an alkyl radical of 1 to 5 carbon atoms,
- R_{11} represents a hydrogen atom or a radical $-Alk-COOR_{12}$ where R_{12} represents a hydrogen atom, an alkyl radical of 1 to 5 carbon atoms or a benzyl radical,
- HetN represents a 5- or 6-membered heterocycle containing at least one nitrogen atom and optionally another heteroatom chosen from nitrogen and oxygen,

optionally in the form of one of their pharmaceutically acceptable salts.

3. Compounds of formula I, according to either of Claims 1 and 2, in which

- **R_1** represents an alkoxy radical of 1 to 5 carbon atoms, a carboxyl radical, a radical -O-Alk-COOH in which Alk represents an alkylene radical of 1 to 5 carbon atoms, a radical of formula -O-Alk-Ph in which Alk represents an alkylene radical of 1 to 5 carbon atoms and Ph represents a phenyl radical which is optionally substituted with one or more halogen atoms or with one or more alkoxy radicals of 1 to 5 carbon atoms or with one or more carboxyl radicals, a radical of formula -NH-CO-Ph or a radical of formula -CO-NH-Ph,
- **R_2** represents an alkyl radical of 1 to 5 carbon atoms,
- **A** represents a radical -CO-,
- **R_3** and **R_4**, which are different, each represent a hydrogen atom, an alkoxy radical of 1 to 5 carbon atoms, an amino radical, a carboxyl radical or an alkoxycarbonyl radical of 2 to 6 carbon atoms,

optionally in the form of one of its pharmaceutically acceptable salts.

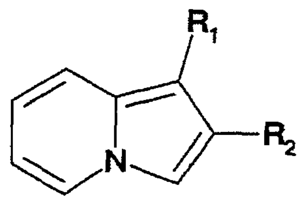
4. Compound of formula I, according to Claim 1, chosen from the following compounds:

- (4-amino-3-methoxyphenyl)(1-methoxy-2-methylindolizin-3-yl)methanone

- 3-(4-amino-3-methoxybenzoyl)-2-methylindolizin-1-yl carboxylic acid
- 2-{[3-(4-amino-3-methoxybenzoyl)-2-methylindolizin-1-yl]oxy}acetic acid
- (4-amino-3-methoxyphenyl){1-[(4-chlorobenzyl)oxy]-2-methylindolizin-3-yl}methanone
- (4-amino-3-methoxyphenyl){1-[(3-methoxybenzyl)oxy]-2-methylindolizin-3-yl}methanone
- 4-({[3-(4-amino-3-methoxybenzoyl)-2-methylindolizin-1-yl]oxy}methyl)benzoic acid
- 3-(4-carboxybenzoyl)-2-methylindolizin-1-yl carboxylic acid
- methyl 3-[(1-methoxy-2-methylindolizin-3-ylcarbonyl]benzoate
- 4-[(1-methoxy-2-methylindolizin-3-yl)carbonyl]benzoic acid

optionally in the form of one of its pharmaceutically acceptable salts.

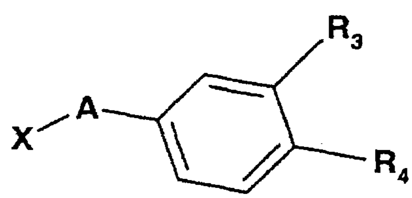
5. Method for preparing the compounds of formula I according to Claims 1 to 4, characterized in that an indolizine derivative of formula II,



(II)

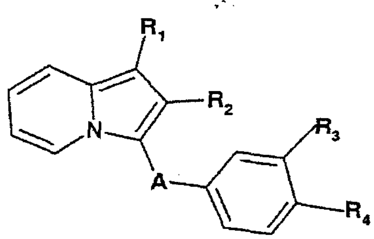
in which R_1 and R_2 have the meaning given for formula I,

is condensed with a derivative of formula III,



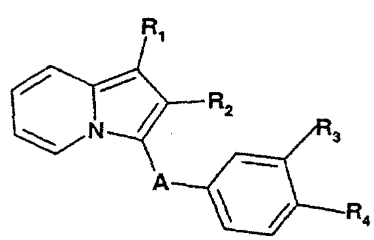
(III)

in which R_3 or R_4, which are identical or different, each represent a hydrogen atom, a nitro radical or an alkoxycarbonyl radical of 2 to 6 carbon atoms, in order to obtain the compounds of formula Ia or Id,



(Ia)

R_3 and/or R_4 = $-NO_2$

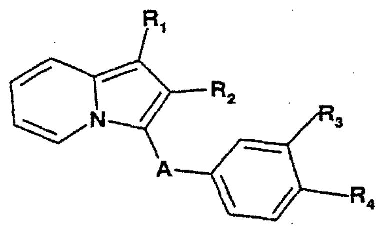


(Id)

R_3 and/or R_4 = $-CO_2$Alkyl

and then,

b) in that the compounds of formula Ia are subjected to a reduction in order to obtain the compounds of formula Ib,



(Ib)

R_3 and/or R_4 = $-NH_2$

in which R_3 and/or R_4 represent an amino radical, which compounds of formula Ib then

- are subjected to the action of an alkyl halide in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical $-NR_5R_6$ (in which R_5 represents a hydrogen atom and R_6 represents an alkyl radical of 1 to 5 carbon atoms) and a radical $-NH-Alk-NR_5R_6$ or a radical $-NH-Alk-COOR_7$ (in which R_7 does not represent a hydrogen atom) from which, by a subsequent saponification, the compounds of formula I are obtained for which R_4 and/or R_3 represent a radical $-NH-Alk-COOR_7$ in which R_7 represents a hydrogen atom,

or

- are subjected to acylation in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical -NH-CO-Alk, or a radical -NH-CO-Alk-NR_9R_{10}, which are then subjected to alkylation in order to obtain a radical -N(R_{11})-CO-Alk or a radical -N(R_{11})-CO-Alk-NR_9R_{10} where R_{11} represents a radical -Alk-$COOR_{12}$ in which R_{12} does not represent a hydrogen atom, the latter compounds are then optionally subjected to saponification in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical -N(R_{11})-CO-Alk or a radical -N(R_{11})-CO-Alk-NR_9R_{10} where R_{11} represents a radical -Alk-COOH,

or

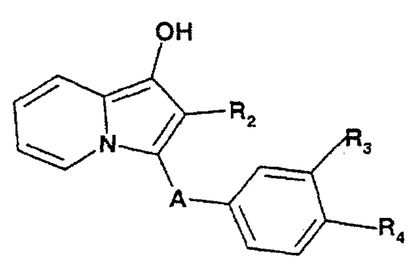
- are subjected to sulphonylation in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical -NH-SO_2-Alk or a radical -NH-SO_2-Alk-NR_9R_{10}, which are then subjected to alkylation in order to obtain a radical -N(R_{11})-SO_2-Alk or a radical -N(R_{11})-SO_2-Alk-NR_9R_{10} where R_{11} represents a radical -Alk-$COOR_{12}$ in which R_{12} does not represent a hydrogen atom, the latter compounds are then optionally

subjected to saponification in order to obtain the compounds of formula I for which R_4 and/or R_3 represent a radical $-N(R_{11})-SO_2-Alk$ or a radical $-N(R_{11})-SO_2-Alk-NR_9R_{10}$ where R_{11} represents a radical -Alk-COOH

f) in that the compounds of formula Id in which R_3 and/or R_4 represent an alkoxycarbonyl radical are subjected to saponification in order to obtain the compounds of formula I in which R_3 and/or R_4 represent a carboxyl radical,

or

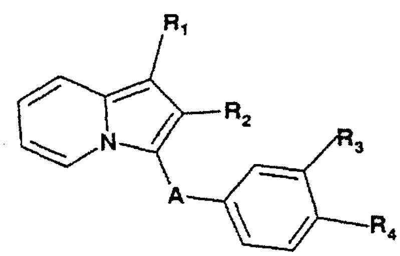
g) in that when R_1 represents a benzyloxy radical, the compounds of formula Ia are subjected to the action of trifluoroacetic acid or the compounds of formula Id to hydrogenation, in order to obtain the compounds of formula If,



(If)

in which R_3 and/or R_4 have the meanings given above,

and then in that the compounds of formula If are subjected to O-alkylation in order to obtain the compounds of formula Ig,

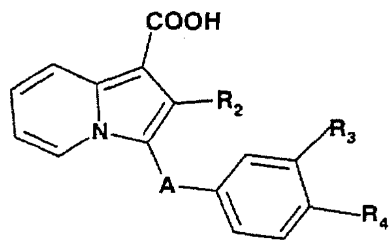


(Ig)

in which R_3 and/or R_4 have the meanings given above, and R_1 represents a linear or branched alkoxy radical of 1 to 5 carbon atoms, a radical $-O-(CH_2)_n$-cAlk, a radical -O-Alk-$COOR_7$, a radical -O-Alk-NR_5R_6, a radical $-O-(CH_2)_n$-Ph, or a radical -O-Alk-O-R_8 – which, when R_8 represents a radical $-COCH_3$, can give, by subsequent saponification, a radical -O-Alk-OH – or a radical -O-Alk-CN which, by treatment with hydroxylamine, gives a radical -O-Alk-$C(NH_2)$=NOH,

or

h) in that when R_1 represents an alkoxycarbonyl radical, the compounds of formula Ia are subjected to saponification in order to obtain the compounds of formula Ih,



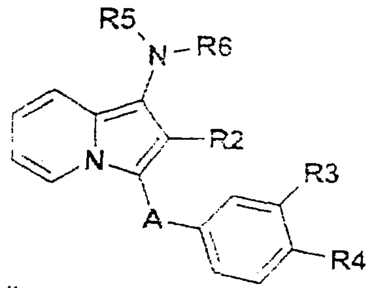
(Ih)

in which R_3 and/or R_4 have the meanings given above, which are then subjected to the action of an amine derivative in order to obtain the compounds of formula I in which R_1 represents a radical -CO-NH-Alk or a radical -CO-NH-Ph, or to the action of an amino acid derivative in order to obtain the compounds of formula I in which R_1 represents a radical -CO-NH-$(CH_2)_m$-$COOR_7$,

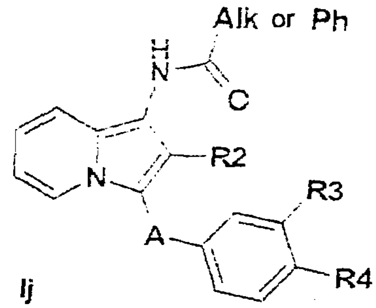
or

i) in that when R_1 represents a radical -NH-CO_2tButyl, the compounds of formula Ia or Id are subjected

- either to alkylation followed by deprotection and an optional second alkylation in order to obtain the compounds of formula Ii,
- or to deprotection, followed by acylation in order to obtain the compounds of formula Ij



Ii



Ij

6. Pharmaceutical composition containing, as active ingredient, a compound of formula I, according to any one of Claims 1 to 4, optionally in combination with one or more inert and appropriate excipients.

7. Pharmaceutical composition according to Claim 6, which is useful in the treatment of diseases requiring modulation of b-FGF.

8. Pharmaceutical composition according to Claim 6, which is useful in the treatment of carcinomas having a high degree of vascularization, such as carcinomas of the lung, breast, prostate and oesophagus, cancers which induce metastases, such as colon cancer and stomach cancer, melanomas, gliomas, lymphomas and leukaemias.

9. Pharmaceutical composition according to Claim 6, which is useful in the treatment of cardiovascular diseases such as atherosclerosis, post-angioplasty restinosis, diseases linked to complications which appear following the fitting of

endovascular prostheses and/or aorto-coronary artery by-pass surgery or other vascular transplants, cardiac hypertrophy, or vascular complications in diabetes such as diabetic retinopathies.

10. Pharmaceutical composition according to Claim 6, which is useful in the treatment of chronic inflammatory diseases such as rheumatoid arthritis or IBDs.

11. Pharmaceutical composition according to Claim 6, which is useful in the treatment of achondroplasia (ACH), hypochondroplasia (HCH) and TD (thanatophoric dysplasia).

12. Use of a compound of formula I according to Claim 1, for the preparation of a pharmaceutical composition which is useful in the treatment of diseases requiring modulation of b-FGF.

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Your file references *(optional)*		SSL0082 / MS	
NATIONAL REGISTRATION NO.		02/04,220	
TITLE OF THE INVENTION (200 characters or spaces maximum)			
Novel 1,2,3-substituted indolizine derivatives, selective inhibitors of b-FGF.			
THE APPLICANT(S):			
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DATE AND SIGNATURE(S) OF THE APPLICANT(S) OR OF THE REPRESENTATIVE (Name and capacity of the signatory) 15 July 2002 Maria SOULEAU PG 9395		[signature]	

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